The association between osteoarthritis and invasive management strategies and clinical outcomes following acute myocardial infarction in electronic health record data

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Declaration

This thesis was undertaken as part of an intercalated degree between the fourth and fifth year of an undergraduate medical degree (MBChB) at Keele University.

The initial idea for this thesis was conceived by Professor Mamas Mamas and Dr. Ross Wilkie.

I was responsible for deriving the search strategy for the included systematic searches with guidance from Dr. Ross Wilkie.

The statistical analyses presented in this thesis were planned with support from Dr. Mohamed Mohamed, Dr. Ross Wilkie, and Professor Mamas Mamas. I was responsible for conducting the statistical analysis and interpreting the results.

Foreword

I started studying medicine at Keele University in 2015 after completing a BSc in mathematics and chemistry at the University of British Columbia in Vancouver, Canada. I have developed a passion for both cardiology and epidemiology during my time studying medicine. I have been awarded a Young investigator Award by the Osteoarthritis Research Society International (OARSI) for my contributions to a project that used mediation analysis within a Cox-proportional hazards model to elucidate pathways through which OA can lead to mortality. I have also been awarded the Wolfson Intercalated Award for academic excellence which has helped fund my intercalated degree. After medical school I will apply for the academic foundation programme, as my ultimate goal is to become an academic cardiologist.

Abstract

Background

The association between osteoarthritis (OA) and acute myocardial infarction (AMI) is unclear, as are the outcomes of people with OA diagnosed with AMI. This study aimed to describe the annual prevalence of OA among AMI patients and describe the association between OA and invasive management strategies and adverse outcomes in AMI patients presenting to secondary care.

Methods

The National Inpatient Sample (NIS) was searched for all AMI hospitalisations between 2004 and 2015. The prevalence of OA among the AMI group was calculated. The proportion of patients receiving invasive management strategies (coronary angiography (CA), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG)) and experiencing adverse clinical outcomes (in-hospital mortality, major acute cardiovascular and cardiovascular events, all-cause bleeding, and stroke or TIA) was compared by OA status. Adjusted binary logistic regression determined the association between OA and each invasive management strategy and adverse clinical outcome.

Results

Of 6,561,940 hospitalizations for AMI between 2004 and 2015, 414,072 (6.3%) had a concurrent OA diagnosis. OA patients were older (mean: 75.3 versus 67.1 years, $p<0.001$) and more likely to be female (55.7% vs. 38.6%, $p<0.001$). OA was associated with a decreased odds of receiving CA (adjusted odds ratio 0.909; 95% confidence interval 0.903, 0.916), PCI (0.873; 0.866, 0.879), and CABG (0.983; 0.971, 0.996). OA was also associated with a decreased odds of adverse clinical outcomes (in-hospital mortality: 0.680; 0.670, 0.691; MACCE: 0.709; 0.699, 0.719; all-cause bleeding: 0.757; 0.741, 0.772; and stroke: 0.844; 0.822, 0.868).

Conclusion

A systematic differential misclassification bias, where unwell patients with OA were less likely to receive an OA code because codes for serious illness took precedence, is likely to explain the unexpected result of OA being associated with better outcomes following AMI. This bias should be considered when using electronic health record data to study the effects of comorbidities in unwell patients.

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List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
ACL	Anterior cruciate ligament
ACS	Acute coronary syndrome
AGE	Advanced glycated end product
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AMED	The Allied and Complementary Medicine Database
AMI	Acute myocardial infarction
APM	Arthroscopic partial meniscectomy
ARB	Angiotensin receptor blocker
BMD	Bone mineral density
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CA	Coronary angiography
CABG	Coronary artery bypass grafting
CASP	Critical Appraisal Skills Programme
CHD	Coronary heart disease
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CiPCA	Consultations in Primary Care Archive

CK-MB	Creatine kinase myocardial band
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
cTn	Cardiac troponin
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DIP	Distal interphalangeal joint
DMOAD	Disease modifying OA drug
DRG	Diagnosis related group
ECG	Electrocardiogram
EHR	Electronic health record
EULAR	European League Against Rheumatism
GDP	Gross domestic product
GRACE	Global Registry of Acute Cardiac Events
HCUP	Healthcare Cost and Utilisation Project
HF	Heart failure
HITECH	Health Information Technology for Economic and Clinical Health
HRT	Hormone replacement therapy
IABP	Intra-aortic balloon pump or ventricular assist device (IABP)

IBD	Inflammatory bowel disease
ICD-10-CM/PCS	International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICF	International classification of functioning, disability, and health
IHD	Ischaemic heart disease
IL1B	Interleukin 1-beta
LDL	Low density lipoprotein
LTAC	Long term acute care hospitals
MACCE	Major acute cardiovascular and cerebrovascular events
MCL	Medial collateral ligament
MeSH	Medical Subject Heading
MI	Myocardial infarction
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MSK	Musculoskeletal
NFKB	Nuclear factor kappa light chain enhancer of activated B cells
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIS	National Inpatient Sample
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non ST-elevated myocardial infarction
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	Odds ratio
PCI	Percutaneous coronary intervention
PIC	Pro-inflammatory cytokine
PICO	Population, intervention/exposure, control, outcome
PIP	Proximal interphalangeal joint
PPV	Positive predictive value
QALY	Quality adjusted life year
QOL	Quality of life
RA	Rheumatoid arthritis
RAGE	Receptor for advanced glycated end products
RCT	Randomised control trial
RR	Relative risk
SASP	Senescence-associated secretory phenotype

SD	Standard deviation
SLE	Systemic lupus erythematosus
SMC	Smooth muscle cell
SPSS	Statistical Package for the Social Sciences
STEMI	ST-elevated myocardial infarction
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TNFA	Tumour necrosis factor alpha
UK	United Kingdom
US	United States
WHO	World Health Organisation
WNT	Wingless integrated pathway

1 Chapter 1: Introduction

1.1 Introduction: OA and AMI

Osteoarthritis (OA) is the most common joint condition and a leading cause of disability globally (Y. Zhang & Jordan, 2010). The global prevalence of symptomatic OA in adults is approximately 10-12% (Hunter et al., 2014) and is expected to rise due to the ageing population and increasing obesity rates (both are risk factors for OA) (Murray et al., 2012). The burden of OA can be measured by disability adjusted life years (DALYs), which was introduced by the Global Burden of Disease study in 1990 and is the sum of the years of life lost and the years lived with disability caused by a particular disease (for example, a person living in good health to their full life expectancy would have 0 DALYs) (Murray et al., 2012). In 2010, OA was responsible for 10% of musculoskeletal DALYs globally (which accounted for 6.8% of all DALYs in 2010), increasing by 64% from 1990 to make it the condition with the second fastest increasing burden (after diabetes) (Murray et al., 2012). The lack of effective disease-modifying OA drugs (DMOADS) and the progressive nature of the condition means that many people with OA will eventually experience joint failure and require surgical interventions such as total joint replacement. In the US, UK, Canada, and France, it is estimated that the total cost of OA is 1-2.5% of these countries gross domestic product (GDP), with joint replacement surgery accounting for 85% of this cost (Hunter et al., 2014). While OA was once thought to be a "wear and tear" disease caused by biomechanical factors such as overuse, excessive loading, and malalignment, there is a growing body of evidence that suggests there to be an inflammatory component to the pathophysiology of OA (Kapoor et al., 2011). This combined with the sharing of risk factors with cardiovascular disease (for example age, obesity, and metabolic syndrome) may suggest a shared pathophysiology between the two conditions.

Cardiovascular disease (CVD), including myocardial infarction (MI), heart failure (HF), stroke, and peripheral vascular disease accounts for up to 40% of all deaths globally, more than any

other cause (Santulli, 2013). Advancements in the identification, management, and primary and secondary prevention of CVD and AMI have led to better patient outcomes in developed countries; however, developing countries still face increasing rates of CVD and AMI incidence and mortality (J. L. Anderson & Morrow, 2017; Sanchis-Gomar et al., 2016). Traditional cardiovascular risk factors include advanced age, obesity, hypertension, smoking, dyslipidaemia, and diabetes mellitus (DM) (Boersma et al., 2003). Similar to OA, there is evidence that systemic inflammation is a risk factor for atherosclerosis and CVD. Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriatic arthritis are associated with an increased risk of both fatal and non-fatal CVD when compared to people without these conditions, even after adjustment for traditional CVD risk factors (Symmons & Gabriel, 2011). There is now further research hypothesising that low-grade inflammation from obesity and normal ageing (called "inflammageing") may also increase the risk of CVD (Gustafson, 2010; Rocha & Libby, 2009). Similar hypotheses have been made between low-grade inflammation and the development of OA, as two of the most potent risk factors for OA are increased age and obesity (Mobasheri & Batt, 2016; Sowers & Karvonen-Gutierrez, 2010). This suggests a shared pathophysiology between OA and CVD, where both conditions may be caused or perpetuated by low-grade inflammation from inflammageing and obesity/metabolic syndrome.

Previous studies have reported an association between OA and overall CVD, however the relationship between OA and specific cardiovascular diseases are less clear (Hall et al., 2016). Ong and colleagues (2013) reported an increased prevalence of MI (8.2% versus 3.7%), heart failure (5.9% versus 2.1%), angina (8.8% versus 2.5%), and stroke (6.8% versus 2.6%) in patients with OA compared to those that did not have OA (Ong et al., 2013). Cross-sectional analysis of patients in Canada also reported an association between OA and any heart disease in crude models (odds ratio (OR) 1.54 95% CI 1.45 to 1.64) and models adjusted for demographic and socioeconomic factors, chronic obstructive pulmonary disease (COPD),

hypertension, and diabetes (adjusted OR 1.45 95% CI 1.36-1.54) (Rahman, Kopec, Cibere, et al., 2013). However, the same study found that OA was only associated with MI in women (adjusted OR 1.49, 95% CI 1.28 to 1.75) and not in men (adjusted OR 1.08, 95% CI 0.91 to 1.28). Because the adjusted and unadjusted odds ratios were similar throughout the analysis, the authors suggest that covariates not included in the analysis, such as inflammation and muscle weakness, may be responsible for the association between OA and CVD and warrant further research. Similarly, a systematic review and meta-analysis in 2016 examining OA and various types of CVD found that OA was associated with heart failure (relative risk (RR) 2.80, 95% CI 2.25 to 3.49) and ischemic heart disease (RR 1.78, 95% CI 1.18 to 2.69), but not with AMI or stroke (Hall et al., 2016).

The overall aim of the work in this thesis was to describe the prevalence of OA in AMI patients over time and to determine the association between OA and invasive management strategies and adverse clinical outcomes in patients presenting to secondary care with a diagnosis of AMI. This chapter will first introduce OA and AMI, followed by a discussion of the links between the two diseases. It will also include a systematic review that was designed to identify published peer-reviewed papers that used EHR to investigate the effect that OA has on patients diagnosed with AMI. The remaining chapters will describe a study which examines whether OA is associated with the management offered to patients diagnosed with AMI and their outcomes using the National Inpatient Sample (NIS), a large electronic record of secondary care visits from the United States.

1.2 Osteoarthritis

1.2.1 Overview of OA

Osteoarthritis was traditionally thought to be non-inflammatory and the result of “wear and tear” of joints that have been damaged through biomechanical factors including overuse, excessive loading, and malalignment. These insults cause the pathognomonic feature of OA,

the progressive and irreversible degradation of articular cartilage. Unlike other tissues, cartilage has minimal reparative capabilities owing to its avascular nature (Mobasheri & Batt, 2016). However, osteoarthritis is now recognised as a “wear and repair” disease, with osteophyte formation (bony protrusions), subchondral plate thickening, and synovial membrane inflammation characterising an aberrant reparative process (Martel-Pelletier, 1999). As the articular cartilage is broken down, there is an accompanied loss of joint space and the presence of cysts and sclerotic tissue within the bone. These disease processes produce pain, stiffness, and a loss of normal joint function, which are the cardinal features of OA.

1.2.2 Definition of OA

The National Institute for Health and Care Excellence defines OA as activity related joint pain in adults over 45 years-old with either no morning stiffness or morning stiffness that lasts less than 30 minutes (National Institute for Health and Care Excellence, 2014). However, people with OA can present with various signs and symptoms in addition to joint pain including joint stiffness, joint deformity, and loss of joint function. Imaging techniques such as radiographs were widely used to diagnose OA, however, this is no longer routinely performed because of the poor correlation between the radiographic and clinical features of OA (Cibere, 2006). Additionally, some people with OA may have radiographic changes including loss of joint space and osteophyte formation and be completely asymptomatic. There is no single presentation or linear progression of OA, as people with OA may be asymptomatic or present with a wide range of signs and symptoms. Additional complexity is added when considering whether a case definition of OA is self-reported or doctor diagnosed. For example, doctor diagnosed OA could mean either the identification of radiographic OA changes or the clinical syndrome of OA. Furthermore, the most widely used radiographic grading system, the Kellgren and Lawrence (K-L) grading system, is defined by relatively ambiguous wording that can further complicate the case definition of OA (Ferguson et al., 2019).

1.2.3 Phenotypes

1.2.3.1 Phenotypes of OA

A phenotype is "the sum total of observable characteristics of an individual, regarded as the consequence of the interaction of the individual genotype and environment" (D. T. Felson, 2010). It is useful to identify phenotypes within a disease because they may imply different causes or mechanisms of the disease and uncover a better understanding of the pathology and effective treatment methods (Dell'Isola et al., 2016). Consider the case where only a specific phenotype (amongst many disease phenotypes) responds well to a treatment. Because the other phenotypes see no response, the therapeutic effect of the new treatment will be diminished and potentially go unrecognised unless the patients are stratified by individual phenotype (D. T. Felson, 2010).

It was once thought that OA was a single disease process resulting in a single phenotype, however, it is now recognised that OA is a heterogeneous disease with many phenotypes and joint failure is the common end-stage clinical presentation (Castañeda et al., 2014). Therefore, it is important to identify distinct phenotypes of OA in order to advance research and potentially find disease modifying OA drugs (DMOADs).

OA phenotypes can be broadly categorised into a clinical syndrome or a radiographic syndrome (Vina & Kwoh, 2018). Distinguishing characteristics of the clinical syndrome include joint pain, joint malalignment, gait disturbances, and other comorbidities. Distinguishing characteristics of the radiographic syndrome include radiographic features of OA (loss of joint space, osteophytes, and subchondral cysts and sclerosis) and MRI-detected lesions. As previously mentioned, there is a relatively poor correlation between the clinical and radiographic syndromes of OA (Cibere, 2006). This implies the existence of many distinct phenotypes of OA which may each benefit from a specific and targeted management plan.

Bijlsma and colleagues (2011) proposed the differentiation of OA into four distinct clinical phenotypes: post-traumatic or repetitive, metabolic, ageing, and genetic (Bijlsma et al., 2011). Each proposed phenotype may potentially affect different age groups, different joints, and may have different treatments. For example, the post-traumatic or repetitive OA phenotype mostly affects the knee, thumb, ankle, or shoulder, while the metabolic OA phenotype is more likely to affect the hand or be generalised. Similarly, the post-traumatic or repetitive OA phenotype may benefit most from joint stabilisation and surgical techniques, while the metabolic OA phenotype may benefit most from weight loss and glycaemic and lipid control (Bijlsma et al., 2011).

1.2.3.2 Identifying further phenotypes

There are two main ways to identify phenotypes in OA (Berenbaum, 2019). The "top-down" approach involves grouping patients based on specific aetiological and risk factors. The idea is that different aetiologies may cause different pathologies and clinical presentations and provide a natural way of grouping patients. The second method is the clinical phenotyping approach, and relies only upon statistical models (cluster analysis) to find clusters of patients based on a set of patient characteristics (for example, the model can consider age, gender, and mobility) (Van der Esch et al., 2015).

An editorial by Castaneda and colleagues used the "top-down" approach to suggest aetiological and pathogenic phenotypes for OA (Castañeda et al., 2014). They suggested reclassifying "primary OA" (idiopathic OA) into one of following three phenotypes (based on risk factors): genetically determined, oestrogen dependent, or age related. They also proposed metabolic and high bone mineral density as two additional phenotypes of OA. They also discuss pathogenic phenotypes, arguing that phenotypes of OA may be determined by the tissue type that is most damaged in the joint. For example, primarily subchondral bone injury may cause a phenotype characterised by pain and bone lesions on magnetic resonance

imaging (MRI), primarily synovium injury may cause an inflammatory phenotype, and primarily soft tissue injury may cause bursitis and tendonitis.

van der Esch (2015) discussed how there was a lack of studies investigating clinical phenotypes of OA, and the few published works on the topic only consider single patient parameters (such as pain or alignment) and not a cluster of characteristics (Van der Esch et al., 2015). This motivated the authors to identify clusters of OA phenotypes in 551 patients based on 4 characteristics (upper leg strength, body mass index (BMI), severity of radiographic OA, and depressive symptoms). Cluster analysis found 5 distinct phenotypes: minimal joint disease, strong muscle, severe radiographic, obese, and depressive symptoms. Promisingly, the same authors had previously performed the same analysis on a different cohort and found 5 similar clusters (Knoop et al., 2011).

Both approaches have their advantages. A "top-down" approach has the benefit of being able to link risk factors with disease processes, helping to uncover disease pathology. Clinical phenotyping has the advantage of clustering patients by easily obtainable measurements and characteristics, thus allowing clinicians to easily identify and treat specific phenotypes. Regardless of how it is accomplished, the identification of evidence-based phenotypes of OA will help identify new treatment methods through randomised control trials (RCT), and hopefully propel OA research towards the development of effective DMOADs.

1.2.4 Epidemiology

1.2.4.1 Prevalence

Osteoarthritis is the most common form of arthritis globally (O'Neill et al., 2018). The most common site of OA is the knee, affecting over 250 million people worldwide. The prevalence of OA is expected to rise due to the ageing population and increasing obesity rates (both are risk factors for OA) (Murray et al., 2012). However, prevalence estimates of OA depend greatly on the definition being used. In the United States, symptomatic (clinical) OA is estimated to affect

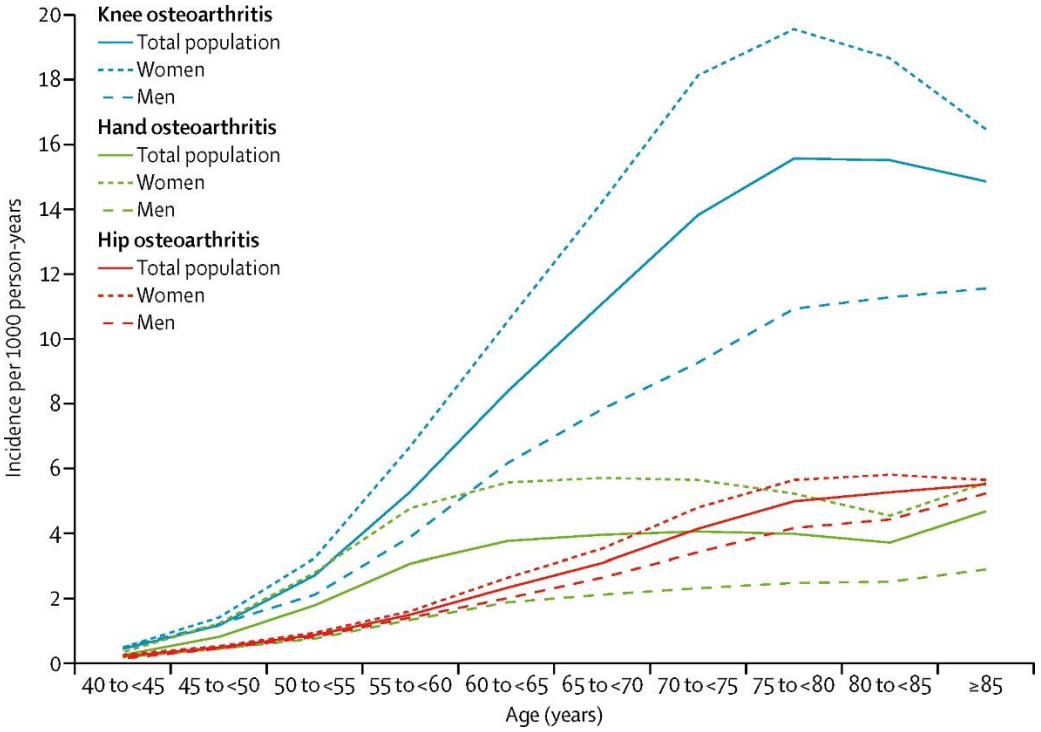
10% of men and 13% of women over 60 years-old (Y. Zhang & Jordan, 2010). Similarly, in a cohort of the Framingham Study of participants aged 63 to 94 years-old, 9.5% had symptomatic knee OA (11.4% women and 6.8% men) (O'Neill et al., 2018). However, the prevalence of radiographic OA is generally higher than the prevalence of symptomatic OA. The same Framingham study reported the prevalence of radiographic OA (defined by at least 2 radiographic changes) to be 33% (34% of women, 31% of men), much higher than their symptomatic OA prevalence estimate. Additionally, the true prevalence of OA may be underestimated because many studies rely on radiographic diagnoses that are insensitive to early disease (O'Neill et al., 2018).

1.2.4.2 Incidence

The overall incidence of OA was measured using the Framingham Cohort Study in Massachusetts. Using data from 20 to 89 year olds, the age and sex matched incidence of knee, hand and hip OA was 240/100,000, 100/100,000, and 88/100,000 person-years respectively (O'Neill et al., 2018).

However, age and sex exert large effects on the incidence on OA. Using general practice registry data, the incidence of OA has been reported to increase rapidly starting from 50 years old, reach a maximum incidence at 75 years old, and progressively decline in adults over 75 years old (Hunter & Bierma-Zeinstra, 2019) (Figure 1.1). Men and women under 55 years-old have a similar risk of developing OA, however, there is a substantially increased risk of incident OA in post-menopausal women compared to men of similar age (O'Neill et al., 2018).

Figure 1.1: The incidence of OA per 100,000 people by age, sex, and site (Hunter & Bierma-Zeinstra, 2019). Reproduced with permission by Elsevier.



1.2.4.3 Risk factors

Risk factors for OA may be categorised as systemic or local. Systemic risk factors include advanced age, obesity, female gender, diet, high bone mineral density, genetic factors, and certain ethnicities. Local risk factors include joint injury, certain occupations, physical activity, muscle weakness, and joint malalignment (Johnson & Hunter, 2014).

1.2.4.3.1 Systemic risk factors

Age is one of the strongest and most well-known risk factors for the development of OA in all joints (Vina & Kwoh, 2018; Y. Zhang & Jordan, 2010). Using data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of radiographic knee OA in males was 27.4% in sexagenarians, 33.5% in septuagenarians, and 40.7% in octogenarians, with women experiencing a similar trend (35.2%, 44.6%, and 55.6% respectively) (Dillon et al., 2006). A comparison of the prevalence of OA between adults 55 to 64 and over 75 years old in the Johnston County Osteoarthritis Project found that the prevalence of radiographic knee OA increased from 26.2% to nearly 50%, respectively, and the prevalence of symptomatic knee OA

increased from 16.3% to 32.8%, respectively (S. Anderson & Loeser, 2010). Y. Zhang and colleagues (2010) proposed that older age is accompanied by cartilage thinning, reduced muscle strength, an accumulation of oxidative damage, and diminished proprioception which leads to increased joint susceptibility when exposed to stress and contributes to the development of OA (Y. Zhang & Jordan, 2010).

Similar to advanced age, being overweight or obese is a strong and well documented risk factors for incident knee OA. A systematic review and meta-analysis of risk factors for OA reported that obesity was strongly associated with incident knee OA (pooled OR 2.63, 95% CI 2.28 to 3.05) compared to non-obese individuals (Blagojevic et al., 2010). A more recent systematic review and meta-analysis similarly reported that compared to normal BMI, being obese (OR 2.66 95% CI 2.15-3.28) and being overweight (OR 1.98 95% CI 1.57-2.2) both increased the odds of experiencing knee pain (Silverwood et al., 2015). These findings may also suggest a dose response with BMI and knee pain and knee OA. Similarly, a 5% weight loss and exercise programmes were shown to reduce pain in established symptomatic knee OA and reduce the incidence of radiographic knee OA (David T. Felson et al., 1992; Messier et al., 2004). The relationship between obesity and hip OA however is less consistent than that of knee OA, as there are conflicting reports of their association in the literature, ranging drastically from no effect all the way to obesity being associated with bilateral radiographic hip OA (O'Neill et al., 2018; Y. Zhang & Jordan, 2010). While the traditional aetiology of hip and knee OA in obese individuals is that increased joint loading causes articular cartilage degradation, a recent systematic review and meta-analysis on hand OA and BMI has found an association between increased BMI and radiographic or clinical OA of the hands (Jiang et al., 2016). The fact that hands are non-weight bearing joints suggests that obesity may also increase the risk of OA through non-biomechanical pathways potentially mediated by low-grade inflammation.

There are differences in the occurrence of OA phenotypes between men and women. A 2005 systematic review and meta-analysis showed that compared to women, men had a lower prevalence of hand and knee OA and a lower incidence of knee and hip OA (Srikanth et al., 2005). Additionally, women, particularly over 55 years-old, experienced more severe knee OA compared to men. This suggests that sex hormones may be responsible for these differences, however, research into the area has provided inconsistent results. Hormonal changes around the time of menopause may contribute to a triggering event that then predisposes post-menopausal women to an increased risk of OA (Wluka et al., 2000). Previous studies have shown that oestrogen bound to oestrogen receptors on human chondrocytes induces pro-inflammatory cytokines and cartilage metabolism (Wluka et al., 2000). However, endogenous hormone levels (measured by age of menarche and menopause and parity) were shown to have no effect on incident OA (Wluka et al., 2000). Studies looking at the effect of hormone replacement therapy (HRT) on OA in post-menopausal women have also demonstrated conflicting results. Wluka and colleagues described how HRT reduced the prevalence and severity of knee OA, however, a more recent RCT of post-menopausal women with heart disease found that there was no difference in knee pain among women taking oestrogen and progesterone HRT versus placebo (Nevitt et al., 2001; Wluka et al., 2000). This highlights the need for further research into explaining why older women are at an increased risk of OA.

Observational studies have shown an association between deficiencies in vitamins D, C, K and selenium and the incidence and progression of OA (O'Neill et al., 2018; Y. Zhang & Jordan, 2010). Vitamin D is of particular interest as it has a large role in bone and cartilage metabolism and homeostasis (Vina & Kwoh, 2018). Multiple observational studies have shown vitamin D deficiency to be associated with a faster rate of progression in established OA (O'Neill et al., 2018; Y. Zhang & Jordan, 2010). This prompted the VIDEO study, a randomised, double blind placebo-controlled trial looking at whether vitamin D supplementation altered the progression of knee OA in people with established disease (Arden et al., 2016). This study concluded that

vitamin D supplementation made no difference in the rate of joint space narrowing nor OA symptoms over a 3-year period, providing evidence that there is no role for vitamin D in the management of OA.

Both cross-sectional and longitudinal studies have shown the association between high bone mineral density (BMD) and OA incidence and prevalence (O'Neill et al., 2018). Additionally, high systemic BMD has been associated with OA of the hand and the formation of osteophytes in subclinical knee OA (Vina & Kwoh, 2018). The mechanism for this remains unclear.

Evidence for a genetic component of OA comes from the fact that there is still a risk of developing OA even after adjusting for the other established risk factors. It is estimated that OA has a 30-65% genetic component (Vina & Kwoh, 2018). Twin studies have reported a heritable component of 40% for hand, 65% for knee, and 70% for both hip and spine OA (O'Neill et al., 2018). A recent review found 21 independent susceptibility loci for hip, knee, and hand OA (Warner & Valdes, 2017). However, this only accounts for approximately 25% of the inherited part of OA, and as such further research is necessary to further uncover genetic links (O'Neill et al., 2018).

There are subtle variations of the phenotype of OA depending on ethnic origin. Data from the Johnston County Osteoarthritis Project showed that African American men and women were more likely to have joint space narrowing and osteophytes on knee radiographs compared to white Americans (Nelson et al., 2010). Radiographic hand OA was shown less common in African Americans compared to white Americans (O'Neill et al., 2018). Additionally, Chinese women experienced significantly more radiographic and symptomatic knee OA than white women (O'Neill et al., 2018).

1.2.4.3.2 Local Risk Factors

Overt joint injury, particularly of the knee, is one of the strongest risk factors for the development of OA (Y. Zhang & Jordan, 2010). Knee injury (most commonly damage to the

anterior cruciate ligament (ACL), medial cruciate ligament (MCL), meniscus, or a trans-articular fracture) accounts for 12% of all cases of knee OA in the United States (Brown et al., 2006). A sudden high impact event can lead to permanent tissue injury and chronic structural changes (O'Neill et al., 2018). From computer-simulated projections, knee injury before 25 years of age carries a 2.5 times increased risk of knee OA and 4 times increased risk of total knee replacement later in life (Suter et al., 2017). Interestingly, the more widespread use of MRI has led to the hypothesis that incidental or asymptomatic knee injury can possibly predispose to the development of OA or be part of the pathogenesis. Englund and colleagues examined knee MRIs from a subset of the Framingham cohort and discovered a higher prevalence of incidental meniscus damage in those with OA (82%) compared to those without (25%) (Englund et al., 2008). This provides evidence that the prevalence of secondary OA may be vastly underestimated and other more reliable phenotypes of OA should be used instead of the "primary versus secondary" classification (D. T. Felson, 2010).

It is well documented that occupations that require repetitive loading of a joint will increase the likelihood of incident OA (O'Neill et al., 2018). This has been demonstrated in farmers who develop hip OA, labourers who use pincer grips who develop distal interphalangeal and proximal interphalangeal OA, and workers who kneel and squat such as electricians who develop knee OA (Y. Zhang & Jordan, 2010). Adjustments in technique and variations in repetitive motions can help prevent this increased risk.

There is an interesting relationship between physical activity and OA. Extreme physical activity has been shown to be a risk factor for OA, as both long distance runners and elite soccer players are at an increased risk of knee OA (Y. Zhang & Jordan, 2010). However, these findings may be confounded by the additional risk of injury from their respective sport. Additionally, a subset of the Framingham cohort that self-reported heavy physical activity (strenuous sports, lifting carrying objects greater than five pounds, or gardening with heavy tools) for greater

than 4 hours per day had a greater odds of knee OA (OR 7.0, 95% CI 2.4-20) compared to those undertaking no daily heavy physical activity (McAlindon et al., 1999). Interestingly, moderate physical activity carried no additional risk of hip or knee OA (O'Neill et al., 2018).

Muscle weakness has been long associated with OA. The previously proposed mechanism is that OA leads to less physical activity, which leads to weakness and atrophy of the muscles (O'Neill et al., 2018). Newer evidence however has shown that muscle weakness is present in early disease and can even predate symptomatic OA (O'Neill et al., 2018). Weak quadriceps muscles have been shown to increase the odds of incident symptomatic knee OA (OR 1.65, 95% CI 1.23-2.21) (O'Neill et al., 2018). Muscle weakness has also been reported as a risk factor for progressing from asymptomatic radiographic OA to symptomatic OA (Y. Zhang & Jordan, 2010). Additionally, among participants with ACL injuries, higher ratios of muscle to fat in the thigh was protective against the development of incident knee OA (Vina & Kwoh, 2018). However, strong quadriceps muscles are not always protective. In the context of joint malalignment, stronger thigh muscles increase the risk of knee OA progression (Y. Zhang & Jordan, 2010).

An uneven distribution of force across a joint, such as with varus (bow-legged) or valgus (knock-kneed) deformities, can cause damage to joints, particularly the knee. While malalignment has been shown to accelerate structural damage and the progression of prevalent knee OA, its effect on incident OA is less clear (Y. Zhang & Jordan, 2010). A study investigating such deformities found that after 30 months, varus deformities were associated with both the progression and incidence of medial (tibiofemoral) OA (OR 3.59, 95% CI 2.62-4.93 and 1.49, 1.06-2.10 respectively), but valgus deformities were associated with lateral compartment OA progression (OR 4.85, 3.17-7.42) but not incidence (L. Sharma et al., 2010). Varus and valgus deformities may not be a risk factor for developing OA, but alternatively a marker of disease severity (Y. Zhang & Jordan, 2010).

1.2.5 Pathophysiology

1.2.5.1 Traditional pathophysiology

Osteoarthritis was traditionally thought to be non-inflammatory, and the result of "wear and tear" of joints that have been damaged through biomechanical factors including overuse, excessive loading, and malalignment. These insults cause the pathognomonic feature of OA, the progressive and irreversible degradation of articular cartilage. Unlike other tissues, cartilage has minimal reparative capabilities owing to its avascular nature (Mobasheri & Batt, 2016). However, osteoarthritis is now recognised as a "wear and repair" disease, with osteophyte formation (bony protrusions), subchondral plate thickening, and synovial membrane inflammation characterising an aberrant reparative process (Martel-Pelletier, 1999). Synovial inflammation leads to the production of matrix metalloproteinases (MMPs), which further breakdown the articular cartilage. This results in loss of joint space, as well as the presence of cysts and sclerotic tissue within the bone due to the inflammatory state of the joint. These disease processes produce pain, stiffness, and a loss of normal joint function.

1.2.5.2 The innate immune system

While biomechanical factors play a major role in OA, the strongest risk factors for the incidence and progression of OA are advanced age and obesity/metabolic syndrome. This prompted researchers to re-evaluate the pathophysiology of OA, and led to the discovery that the innate immune system plays a major role in the development and progression of OA (Kapoor et al., 2011). The major drivers of these recently discovered pathways are the cytokines tumour necrosis factor alpha (TNFA) and interleukin one beta (IL1B), key mediators of the body's inflammatory cascade.

Studies have shown that compared to people without OA, those with OA have elevated levels of TNFA and IL1B and their corresponding receptors in their synovial fluid and membrane, articular cartilage, and subchondral bone (Kapoor et al., 2011). These cytokines activate

intracellular signalling pathways (such as nuclear factor kappa light chain enhancer of activated B cells (NFKB) and the Wingless integrated (WNT) pathways) in chondrocytes and other joint tissues (Kapoor et al., 2011). These pathways cause the release of MMPs, enzymes that potently degrade articular cartilage (Kapoor et al., 2011). In addition to MMPs these tissues also release pro-inflammatory cytokines (PICs) including TNFA, IL1B, and interleukin 6 (IL6). These cytokines go on to release more MMPs and PICs, creating a vicious cycle of PICs, MMPs, and progressive cartilage destruction (Kapoor et al., 2011).

Another consequence of PICs in a joint is they can drive the conversion of normally senescent chondrocytes into chondrocytes exhibiting a senescence-associated secretory phenotype (SASP) (Mobasheri & Batt, 2016). All healthy cells eventually undergo replicative senescence, after which they cease to have replicative function. However, in the presence of inflammation, senescent chondrocytes can acquire SASP and secrete a high number of cytokines and MMPs which further accelerates cartilage degradation (Berenbaum, 2013).

1.2.5.3 Sources of Inflammatory markers in people with OA

Given the last sections discussion of how damaging an inflammatory state can be to joints, the natural next question is what causes a person to be in an inflammatory state? Mobasheri (2016) discussed the concept of "inflammaging" as a source of PICs that can initiate cartilage degradation. Normal ageing is associated with an underlying low level of PICs that are present in people's bodies at all times (Mobasheri & Batt, 2016). These PICs may initiate the OA disease process by stimulating chondrocytes to release MMPs and more PICs (Mobasheri & Batt, 2016). This would explain why age is one of the strongest risk factors for developing OA. Similarly, inflammaging may also act as the trigger for other age-related diseases including atherosclerosis and cardiovascular disease.

Another potential source of inflammation that may trigger the cascade of cartilage destruction in OA is from obesity and metabolic syndrome. Despite traditionally being thought of as an

inactive store of energy, adipose tissue plays a major role in paracrine and endocrine signalling (Sowers & Karvonen-Gutierrez, 2010). Adipose tissue consists of adipocytes, resident macrophages, and fibroblasts (Berg & Scherer, 2005). Adipocytes also release hormones called adipocytokines, which are leptin, resistin, and adiponectin (Sowers & Karvonen-Gutierrez, 2010). Obesity alters the phenotype of adipocytes in three ways that may trigger the development of OA (Gustafson, 2010). An obese phenotype causes an attenuated release of adiponectin. Adiponectin normally has an anti-inflammatory role by decreasing the amount of TNFA that adipocytes release (Gustafson, 2010). The obese phenotype of adipocytes releases less adiponectin, and therefore promotes an inflammatory environment (Gustafson, 2010). An obese phenotype also causes the release of more leptin. Leptin, the satiety hormone, is often elevated in obese individuals because they become resistant to its effects (analogous to and often co-existing with insulin resistance) (Sowers & Karvonen-Gutierrez, 2010). Leptin receptors have been discovered on chondrocytes, therefore, high levels of leptin may stimulate chondrocytes to release MMPs and PICs into the synovium (Sowers & Karvonen-Gutierrez, 2010), potentially causing cartilage destruction. Finally, obesity causes increased PIC release from adipocytes. Adipocytes have retained their evolutionary capability to release PICs (TNFA, IL1B) and acute phase reactants (such as C-reactive protein (CRP)) in certain conditions (Berg & Scherer, 2005). Studies have reported serum levels of CRP and other PICs to increase correspondingly with increasing BMI (Berg & Scherer, 2005). Additionally, weight loss has been shown to reduce previously high levels of such inflammatory markers, providing further evidence that obesity may be the source of systemic low-grade inflammation necessary to initiate OA (Berg & Scherer, 2005).

Another potential mechanism for the generation of underlying inflammation is through the formation of advanced glycated end products (AGEs). AGEs are proteins created by a persistently hyperglycaemic environment and promote atherosclerosis and CVD (Sowers & Karvonen-Gutierrez, 2010) through the action of its membrane bound receptor (RAGE).

Interestingly, RAGEs have been discovered on the surface of chondrocytes and been shown to induce the release of PICs (Sowers & Karvonen-Gutierrez, 2010). These PICs can then potentially go on and initiate a cascade of events that can lead to OA.

This discussion highlighted an updated pathophysiology of OA with consideration for an inflammatory component of the disease process. Next is a discussion of the clinical features of OA.

1.2.6 Clinical Features

Signs of OA include crepitus, restricted movement, bony enlargement, joint effusion, tenderness on palpation and pain on joint movement. Symptoms of OA include joint pain that increases with activity, joint stiffness, reduced function, joint locking, and the feeling of a joint "giving way". These signs and symptoms tend to be clustered into distinct phenotypes and present differently to medical practitioners. These include but are not limited to an inflammatory phenotype (characterised by synovitis and joint effusion), a chronic pain phenotype, a metabolic phenotype (characterised by metabolic syndrome), and a potentially asymptomatic phenotype that may be characterised only by radiographic and MRI features of OA (Castañeda et al., 2014; D. T. Felson, 2010).

In 2010, the European League against Rheumatism (EULAR) published an evidence-based recommendation for the diagnosis of knee osteoarthritis. They concluded that for knee OA, the three most diagnostic symptoms are persistent knee pain, limited morning stiffness and reduced function, and the three most diagnostic signs are crepitus, restricted movement and bony enlargement (W. Zhang et al., 2010).

Joint pain is the most common symptom of OA, and accounts for a large proportion of disability associated with OA (Heidari, 2011). Joint pain is often the first symptom people with OA notice and is often the triggering factor that causes them to seek help from primary care (Bijlsma et al., 2011). Joint pain is worse during and immediately following exercise and better

following rest (Heidari, 2011). The type of the pain varies; people often experience a chronic dull ache, with superimposed flare-ups of sharp pain (Bijlsma et al., 2011). As discussed previously, chondrocytes are avascular and lack innervation. Therefore, it is hypothesised that joint pain in OA originates from the highly innervated subchondral bone (Glyn-Jones et al., 2015). Because relatively mild disease may not yet reach the innervated bone, by the time a person present with pain they may already have advanced or irreversible OA (Glyn-Jones et al., 2015). Alongside joint pain, joint stiffness is a common symptom of OA. The joint stiffness is caused by synovial inflammation and often follows periods of prolonged inactivity, such as sleeping (Sellam & Berenbaum, 2010). During assessment in clinical practice, a key differentiator between OA and inflammatory arthritis is that in OA, morning joint stiffness often lasts less than 30 minutes (Heidari, 2011). A third common symptom of OA is the loss of joint function causing disability and activity limitation. This can greatly impact the lives of people with OA and is another major reason for consultation (Bijlsma et al., 2011). Knee and hip OA can affect one's ability to walk and climb stairs, and hand OA can make simple tasks such as household chores extremely difficult (Bijlsma et al., 2011). Additionally, symptomatic OA may also be associated with multimorbidity including cardiovascular disease, peptic ulcer disease, or psychological disorders (Swain et al., 2019; Vina & Kwoh, 2018).

Crepitus is a common sign of an arthritic joint and is elicited by passively moving a joint and listening for crackles or a popping sound (W. Zhang et al., 2010). Knee crepitus has been associated with osteophytes and pathology to the meniscus and MCL and may be caused by osteophytes or osseous surfaces rubbing against soft tissue, cartilage, or bone (Crema et al., 2011). Another common sign is restricted joint movement, often caused by synovial inflammation leading to joint stiffness (Sellam & Berenbaum, 2010). The inability for a joint to perform a full range of motion often leads to impaired function. Finally, joint deformity tends to worsen with OA severity, can affect any joint, and is part of a group of bone changes in OA including new bone formation at the joint margin (osteophytes), subchondral bone sclerosis,

and subchondral bone cysts (A. R. Sharma et al., 2013). Bony deformity is commonly seen in the distal (DIP) and proximal (PIP) interphalangeal joints and are called Heberden's and Bouchard's nodes, respectively. These deformities are linked to aberrant attempts to repair joint damage and may further impair a joints range of motion.

1.2.7 Management

1.2.7.1 Conservative Management

The management of OA requires a biopsychosocial approach because OA is associated with many other extra-articular symptoms including poor sleep and depression. The treatment of articular symptoms is stepwise starting with conservative measures, followed by pharmacological and sometimes surgical interventions. A number of conservative measures have been proven efficacious for the management of OA symptoms. Clinicians should sign-post patients to sources of information, advice, and support, including the Arthritis Research UK and National Health Service (NHS) choices websites (National Institute for Health and Care Excellence, 2014). A 5% weight loss for overweight and obese people has been shown to improve pain and functional symptoms (McAlindon et al., 2014). Other conservative treatment options with little or no risk of adverse side effects include muscle strength training (particularly of the quadriceps for knee OA), low impact aerobic exercise, foot orthoses, and knee braces for instability (Mcalindon et al., 2014).

1.2.7.2 Pharmacological management

The National Institute for Health and Care excellence (NICE) advises the use of oral paracetamol and topical non-steroidal anti-inflammatory drugs (NSAIDs) as first line analgesics for people with OA. Regular paracetamol however has been associated with slightly increased risk of gastrointestinal events and multi-organ failure, and as such a person's comorbidities must always be considered (McAlindon et al., 2014). If these measures are ineffective in treating pain, NICE recommends the addition of oral NSAIDs.

Oral NSAIDs are effective in pain relief, however they have potentially serious side effects including gastrointestinal tract ulcers, reductions in glomerular filtration rate, and cardiovascular risks including hypertension, myocardial infarctions, and strokes (Varga et al., 2017). Regular NSAID use has been associated with an increased risk of cardiovascular disease in people with OA. A recent prospective cohort study used marginal structural modelling within a cox-proportional hazards model and determined that NSAID use mediated 41% of the total effect of OA on incident CVD (total effect adjusted hazard ratio: 1.23; 95% CI 1.17 to 1.28) (Atiquzzaman et al., 2019). The authors also found NSAID to mediate the relationship between OA and congestive heart failure (23%), ischemic heart disease (56%), and stroke (64%).

To mitigate the gastrointestinal risks associated with NSAIDs, the OARSI guidelines for the management of OA suggest that NSAIDs be prescribed with a proton pump inhibitor if a patient has a moderate comorbidity risk profile (McAlindon et al., 2014). They advise against oral NSAIDs in patients with a high comorbidity risk profile.

If oral NSAID therapy is ineffective, NICE recommends the use of oral codeine or topical capsaicin for pain relief. Transdermal opiates and intra-articular steroid injections are used for short-term relief of severe symptoms (National Institute for Health and Care Excellence, 2014). Pharmacological therapies with no proven effect as a DMOAD include glucosamine and chondroitin, while the effects of risedronate as a DMOAD are still uncertain (McAlindon et al., 2014).

1.2.7.3 Surgical Management

The lack of effective DMOADs means that the failure of conservative and pharmacological management may lead to joint failure requiring surgical intervention. NICE recommends that people should be referred to an orthopaedic surgeon when the symptoms of OA are resistant to primary care management and significantly impact a person's quality of life (National

Institute for Health and Care Excellence, 2014). There are three main categories of surgical procedures: arthroscopy, osteotomy, and total joint replacements.

Since its inception in the 1980's, arthroscopic debridement and lavage quickly became the standard treatment for symptomatic knee OA, despite the lack of peer-reviewed evidence in its favour (Katz et al., 2010). Arthroscopy is the insertion of a small camera into the joint, allowing surgeons to smooth the articular surface and shave osteophytes (debridement) and remove particulate matter such as of calcium deposits and fragments of cartilage (lavage) (Kirkley et al., 2008). The first RCT looking at the efficacy of knee arthroscopy found no difference in outcomes for 180 patients after 2 years when comparing each of debridement, lavage, and a sham procedure (Moseley et al., 2002). A subsequent RCTs compared arthroscopic debridement, lavage, physical therapy, and medical therapy with only physical and medical therapy and found that after 2 years arthroscopy provided no additional benefit (Kirkley et al., 2008). There are conflicting reports on the efficacy of arthroscopic partial meniscectomy (APM) in patients with knee OA and a meniscus tear, as some reports show APM to increase the rate of progression of OA, however this may be confounded by the direct effects of the tear itself (Katz et al., 2010). NICE recommend against the referral for arthroscopic debridement and lavage for the treatment of OA except for when there is a clear history of mechanical locking of the knee (National Institute for Health and Care Excellence, 2014).

Osteotomies can be performed in patients with unicompartmental knee OA (that often coexists with varus or valgus deformities) when other management strategies have failed (Brouwer et al., 2014). They are also performed in patients too young for a total knee replacement. The aim is to realign the knee in order to distribute force evenly across its surface. As discussed previously, malalignment is a strong risk factor for the progression and possibly incidence of OA. Osteotomies aim to prevent this progression of OA and relieve joint

pain (Katz et al., 2010). If a patient were to present with medial compartment knee OA and an associated genu varus deformity, a surgeon would shorten the lateral tibia (called a valgus osteotomy) in order to distribute more force onto the lateral compartment, thus reducing the force on the already damaged medial compartment and hopefully prevent further OA progression (Brouwer et al., 2014). Osteotomies have a lower success rate and carry a greater risk of revision surgery compared to replacement surgery (Katz et al., 2010). A meta-analysis found that 16% of patients who underwent a valgus high tibial osteotomy required knee arthroplasty within 12 years (Bennell et al., 2012). As such, the gold standard for advanced OA in older patients is a total joint replacement (Katz et al., 2010).

For older patients with advanced OA characterised by pain, functional limitation, or reduced quality of life, joint arthroplasty is the recommended intervention (Bennell et al., 2012). Joint arthroplasty was once viewed as a last resort for advanced OA, however emerging evidence that post-operative function is dependent on pre-operative function highlights some of the benefits of earlier surgery (Katz et al., 2010). However, because implants can be worn down and revision arthroplasty is less successful than primary arthroplasty, patients under 60 are usually not offered replacement surgery (Bennell et al., 2012). Overall, the number of total joint replacements performed is on the rise. In the United States (US) in 2007, there were 550,000 knee replacements, 250,000 hip replacements, and 23,000 shoulder replacement surgeries performed (Katz et al., 2010). This number is expected to rise, as it is estimated there will be 3 million joint replacements in the US by 2030 (Katz et al., 2010). Joint replacement of the ankle and wrist are relatively uncommon due to their relatively low incidence, and the proven efficacy of arthrodesis in these joints (Katz et al., 2010).

1.2.8 Burden of OA

1.2.8.1 Activity limitation and social participation

Osteoarthritis exerts both an individual and a socioeconomic burden. A large individual burden is felt due to the chronic and progressive nature of OA (Hunter et al., 2014). This burden is often felt through activity limitation and participation restriction, which is defined by the World Health Organisations (WHO) International Classification of Functioning, Disability and Health (ICF) as difficulties in executing activities or problems in the involvement of life situations (World Health Organisation, 2007). Specific activities defined by the ICF that may be affected by OA include mobility, self-care, household tasks, work and employment, and recreation and leisure (World Health Organisation, 2007). Eighty percent of people with knee OA have some limitation, 25% cannot perform major activities of daily living, and 11% require personal care (Hunter et al., 2014). Additionally, OA is the most common reason for adults over 65 years-old to have difficulty walking or climbing stairs (Hunter et al., 2014).

1.2.8.2 Quality of life

People with OA also experience a greatly reduced quality of life (QOL), which is measured by alterations to one's physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing, development, and activity compared to people in the same social or cultural group (Felce & Perry, 1995). Quality adjusted life years (QALYs) are a measure of QOL and is the product of the length of life (in years) and the quality of life (ranging from death (0) to perfect health (1)) (Sassi, 2006). For example, 1 year of perfect QOL and 2 years lived at fifty percent QOL would both equal 1 QALY. Disability adjusted life years (DALYs), introduced by the Global Burden of Disease study in 1990, are a composite measurement of the burden of a disease (Murray et al., 2012). DALYs are the sum of the years of life lost and the years lived with disability caused by a particular disease (for example, a person living in good health to their full life expectancy would have 0 DALYs) (Murray et al., 2012). QALYs and DALYs are complements of each other. For the example of a person with an 80-year life expectancy:

$$\#\ of\ QALYs\ +\#\ of\ DALYs = 80\ years.$$

In the United States, 15 million QALYs are lost annually due to OA, a similar number of QALYs lost due to cardiovascular disease and cancer (Hunter et al., 2014). Globally, musculoskeletal (MSK) disorders accounted for 6.8% of all DALYs in 2010, increasing from 4.7% in 1990 (Murray et al., 2012). OA in particular accounted for 10% of all MSK related DALYs in 2010 and had increased by 64% compared to estimates from 1990 (this was the 2nd fastest increasing burden, only next to diabetes) (Hunter et al., 2014).

1.2.8.3 Association with comorbidity

Osteoarthritis is associated with comorbidity. A recent systematic review and meta-analysis of 42 studies examining the association of comorbidities with OA found that people with OA were more likely to have at least one comorbidity compared to people without OA (67% (95% CI 57% to 74%) versus 56% (95% CI 44% to 68%)) (Swain et al., 2019). The same review also found that people with OA had an increased prevalence of stroke (prevalence ratio 2.6; 95% CI 2.1 to 3.2), peptic ulcer disease (PR 2.4; 95% CI 1.7 to 3.3) and metabolic syndrome (PR 1.9; 95% CI 1.2 to 3.1). People with OA were also significantly associated with psychological conditions (PR 1.8; 95% CI 1.2 to 2.5) and any cardiovascular disease (PR 1.6; 95% CI 1.3 to 1.9). A recent meta-analysis found that OA was associated with cardiovascular disease and incident AMI (Schieir et al., 2017). Additionally, symptomatic knee OA has been associated with an increased all-cause and cardiovascular specific mortality (Kluzek et al., 2016).

1.2.8.4 Socioeconomic burden

OA also exerts a large direct and indirect socioeconomic burden. OA is the most common indication for total hip or knee replacements (Y. Zhang & Jordan, 2010), with 185,000 primary hip or knee replacements in the UK in 2016. In the US, United Kingdom (UK) Canada, and France, it is estimated that 1-2.5% of the GDP of these countries is spent on OA, with joint replacement surgery accounting for 85% of this cost (Hunter et al., 2014). The average annual

direct cost of OA per person in Canada was USD $12,000 in 2002 (Hunter et al., 2014). Direct cost estimates in the US vary greatly (depending on whether healthcare resource categories were measured from claims data or survey data), ranging between $1,442 and $21,335 per person per year (Vina & Kwoh, 2018). Indirect costs are much greater than direct costs, and are comprised of sick days, early mortality, and early retirement. The cost of employees being absent from work due to OA is estimated at $10 billion per year, comparable to asthma ($5 billion), migraines ($12 billion), and hypertension ($18 billion) (Hunter et al., 2014).

1.3 Acute myocardial infarction

1.3.1 Overview

Cardiovascular disease (CVD) encompasses any disease that affects the heart or blood vessels (World Health Organisation, 2020). Common subtypes of CVD include coronary heart disease (CHD), strokes and transient ischemic attacks (TIAs), peripheral artery disease, aortic disease, heart failure and cardiomyopathy, and valvular disease. Globally, CVD accounts for up to 40% of all deaths, more than any other cause (Santulli, 2013). While advancements in the identification, management, and prevention of CVD has led to better patient outcomes in developed countries, developing countries still face increasing rates of CVD, including increasing AMI incidence and mortality (Sanchis-Gomar et al., 2016).

1.3.2 Definitions

1.3.2.1 Myocardial injury

Myocardial injury is necessary but not sufficient for a diagnosis of myocardial infarction. Myocardial injury can be reliably detected by certain serum biomarkers such as cardiac troponin. The current definition of myocardial injury is a single cardiac troponin (cTn) level greater than the 99th percentile upper reference limit (J. L. Anderson & Morrow, 2017); acute injury is defined as a rise and fall of cTn as determined by serial measurements (Thygesen et al., 2019). Myocardial injury results in the release of cardiac enzymes (cardiac troponin I (cTn I)

and cardiac troponin T (cTn T)) into the serum (J. L. Anderson & Morrow, 2017). Cardiac troponins are part of the contractile apparatus in myocytes and are highly specific and sensitive to the heart (Thygesen et al., 2019). Elevated levels of these biomarkers can be detected via high sensitivity cTn assays. Creatine kinase myocardial band (CK-MB) is also specific to myocardial injury and used to be the preferred biomarker for myocardial injury, however, because of CK-MB's relative lack of sensitivity (resulting in missed diagnoses) and the overall higher sensitivity and specificity of cardiac troponin, CK-MB has fallen out of favour in most healthcare services (Boersma et al., 2003).

The many different causes of myocardial injury can be grouped into four main aetiologies (Thygesen et al., 2019). The first category of myocardial injury is due to decreased myocardial perfusion. Causes include coronary emboli, coronary vasospasm, shock, and severe anaemia. The second category of injury is due to increased myocardial oxygen demand, including sustained tachycardia and severe hypertension. The third category of injury is due to cardiac conditions such as cardiomyopathies, myocarditis, coronary procedures, and heart failure. The fourth and final category of myocardial injury is due to systemic conditions such as sepsis, chronic kidney disease, pulmonary embolisms, and stroke. It is the clinicians challenge and responsibility to distinguish these causes of myocardial injury from a myocardial infarction.

1.3.2.2 Myocardial Infarction

According to the fourth universal definition of myocardial infarction, an acute myocardial infarction (AMI) is defined as acute myocardial injury (a serum cardiac troponin level greater than the 99th percentile upper reference limit and a rise and fall of serial cTn measurements) and one associated clinical, pathological, or anatomical feature (Thygesen et al., 2019). Associated features include the signs and symptoms of an MI, new ischemic electrocardiogram (ECG) changes, pathological Q-waves, imaging showing the loss of viable myocardium in a pattern consistent with ischemia, or the identification of a coronary thrombus by angiography

or autopsy (Thygesen et al., 2019). Therefore, a detailed history, clinical examination, and investigations are required for a diagnosis of AMI.

1.3.2.3 Sub-types of MI

There are six sub-types of AMI, however all of them share the common endpoint of acute myocardial necrosis (J. L. Anderson & Morrow, 2017). Type 1 AMIs are the most common subtype and are caused by an acute atherothrombosis of an atherosclerotic plaque in a coronary artery. The atherosclerotic plaque undergoes rupture or erosion followed by immediate thrombus formation over the plaque. The resulting atherothrombosis causes coronary artery occlusion and downstream myocardial infarction (Thygesen et al., 2019). Type 2 AMIs are not caused by an acute atherothrombotic event, but instead by situations where myocardial oxygen demand is greater than myocardial oxygen supply (Thygesen et al., 2019). Common causes of myocardial supply and demand imbalances include stable atherosclerotic plaques, coronary artery vasospasm (commonly from cocaine use), and anaemia from massive bleeds. Type 3 AMIs are infarctions causing sudden death without prior ECG or biomarker confirmation of AMI (J. L. Anderson & Morrow, 2017). Type 4a AMIs occur around the time of percutaneous coronary intervention (PCI), type 4b AMIs occurs due to thrombosis of a coronary stent, and type 5 AMIs are infarcts related to coronary artery bypass grafting (CABG) (J. L. Anderson & Morrow, 2017). In addition to these six subtypes, AMIs may also be classified by the presence or absence of ST-segment elevation on ECG; the importance of this classification with respect to management will be discussed further in section 1.3.6.

1.3.3 Pathophysiology

1.3.3.1 Atherosclerosis as the primary cause of AMI

Atherosclerosis is the primary disease process of most cardiovascular diseases. Most AMIs are due to acute atherothrombotic events, where an atherosclerotic plaque is disrupted and an acute thrombus forms over the newly formed and highly thrombogenic surface (Boersma et

al., 2003). Atherosclerosis is a process initiated by endothelial activation and is characterised by a slow and progressive narrowing of large arteries and an accumulation of lipids and cellular debris in the sub-endothelium (Sakakura et al., 2013). Atherosclerosis can start to develop as early as childhood and adolescence. The initiating step in atherosclerosis is activation of the endothelium through a variety of insults, commonly hypertension, smoking, hyperglycemia, or hypercholesteremia (Santos-Gallego et al., 2014). Once activated, the endothelium displays different characteristics to a normal endothelium, particularly, an activated endothelium is more permeable to low density lipoproteins (LDL) and expresses an increased numbers of adhesion proteins that promote monocyte and lymphocyte extravasation (Santos-Gallego et al., 2014). LDL extravasates through the endothelium into the subendothelium where it becomes oxidised by resident macrophages. Oxidised LDL is highly inflammatory, stimulating the release of PICs from macrophages and smooth muscle cells (SMC) (Santos-Gallego et al., 2014). PICs cause pathological thickening of the tunica intima and the proliferation of SMCs. This process does not initially reduce blood flow through the blood vessel, as coronary arteries can undergo outward remodelling to preserve cross sectional area. This produces a prolonged asymptomatic phase in coronary artery disease (Boersma et al., 2003). Over time, macrophages change phenotype to foam cells due to persistent LDL phagocytosis (Sakakura et al., 2013). These foam cells become the fatty streak, which is the earliest atherosclerotic lesion. Foam cells release further PICs that perpetuate the atherosclerotic process. This process causes the proliferation and migration of SMCs, which produce a fibrous cap to stabilise the atherosclerotic lesion (Ferrucci & Fabbri, 2018). Over time, intimal thickening and the accumulation of lipids and cellular debris eventually results in the narrowing of the blood vessel, which reduces blood flow beyond the plaque. The fibrous cap tends to become weaker and thinner over time, predisposing to disruption, thrombosis, and an acute myocardial infarction (Santos-Gallego et al., 2014).

1.3.3.2 Atherosclerosis associated with inflammatory diseases

In addition to the previously mentioned risk factors for the development of atherosclerosis, there is a growing body of evidence that systemic inflammation plays a role in atherosclerotic development and progression. This is evident in chronic autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), seronegative spondyloarthropathies, and inflammatory bowel disease (IBD), all of which have been associated with an excess cardiovascular risk compared to people without these conditions (Steyers & Miller, 2014). People with RA and SLE have been most extensively studied and it has been shown that they have an increased incidence of both fatal and non-fatal CVD when compared to controls (Symmons & Gabriel, 2011). One study showed that over 50% of premature deaths among RA patients were attributed to CVD, and this excess risk is not accounted for by traditional cardiovascular disease risk factors (Symmons & Gabriel, 2011). Similarly, a 2001 cohort study compared the incidence of cardiovascular events in RA patients with those without RA and found an increased incidence rate ratio in the RA group (3.17, 1.33-6.36) even after adjusting for traditional cardiovascular disease risk factors (Del Rincón et al., 2001).

Given this association between chronic inflammation and CVD, further research has looked into why this association exists. These works have suggested that inflammation induced endothelial activation may be a potential mediator of the relationship. A normal endothelium regulates vascular tone (constriction and dilation) and regulates cellular adhesion and thrombosis on the endothelium (via the expression of adhesion molecules and changing its permeability) (Steyers & Miller, 2014). Endothelial cells can be “activated” by a number of stimuli, including PICs from an inflammatory response (Steyers & Miller, 2014). Activated endothelium has a different phenotype that is characterised by increased cellular adhesion, increased permeability, and an increased risk of thrombosis (Steyers & Miller, 2014). One of the first papers describing endothelial activation as a mediator of CVD in patients with RA was

published in 2002. Bergholm and colleagues showed that newly diagnosed RA patients had an impaired vasodilatory response to acetylcholine, suggesting an impairment of the endothelial nitric oxide synthase pathway in RA patients (Bergholm et al., 2002). It is proposed that inflammatory mediators (particularly TNFA) cause endothelial activation by impairing vasodilation via the inhibition of nitric oxide release and by activating transcription factors such as NFKB which in turn increase endothelial permeability and increase the number of adhesion molecules on the surface (Steyers & Miller, 2014). The result of an activated endothelium is the promotion of atherosclerosis, and eventually cardiovascular disease.

1.3.3.3 Atherosclerosis and low-grade inflammation from ageing and obesity

Given the previously discussed association between autoimmune diseases, inflammation and CVD, there is interest in whether low levels of inflammation can stimulate or perpetuate the atherosclerotic process and predispose individuals to CVD. The previous section outlined how inflammation from both obesity and ageing (which are also potent risk factors for CVD) can predispose individuals to developing OA. Next is a discussion of how these two risk factors may promote atherosclerosis and CVD, followed by a proposed potentially shared pathophysiology between OA and CVD.

As discussed previously, inflammageing is the accumulation of cytokines and inflammatory mediators with normal ageing. Age is a strong risk factor for CVD, but there is debate surrounding whether inflammageing causes CVD, or if the associated inflammation is simply a marker of CVD (Ferrucci & Fabbri, 2018). A randomised control trial promisingly showed that low dose (0.5 mg/day) colchicine (an anti-inflammatory) significantly reduced the incidence of acute coronary syndrome in people with stable coronary heart disease (CHD) (Nidorf et al., 2013). There are proposed mechanisms for how low-grade inflammation can predispose to atherosclerosis and CVD. In an inflammatory environment, vascular SMCs are predisposed to undergo early replicative senescence (Ferrucci & Fabbri, 2018). This means that the normally

proliferating SMCs can no longer produce an extra-cellular matrix that supports the fibrous cap, thus predisposing to a weaker plaque that is more prone to rupture (Ferrucci & Fabbri, 2018). Additionally, in a similar fashion to chondrocytes, PICs may induce the senescence-associated secretory phenotype (SASP) from normally senescent SMCs (Ferrucci & Fabbri, 2018). SMCs with SASP secrete MMPs which can further destabilise the fibrous cap of an atherosclerotic lesion and promote acute atherothrombotic events.

The association between obesity and atherosclerosis has been known for decades, however, the mechanism linking them has changed drastically over recent years. Obesity and atherosclerosis were both once thought to be lipid storage disorders (Rocha & Libby, 2009), however, it is now well known that they both have substantial inflammatory components. The function of adipose tissue is no longer thought to be solely insulation and the storage of free fatty acids. It is now recognised to have an essential role in insulin sensitivity, hunger, inflammation, and the development of metabolic syndrome (Gustafson, 2010). Normal adipocytes secrete a number of cytokines. One of which is adiponectin, which plays an important role in attenuating inflammation (by decreasing adipocyte TNFA release), discouraging atherosclerosis (by inhibiting foam cell production and promoting nitric oxide release) and preventing intima media thickening (Gustafson, 2010). Normal adipocytes are capable of releasing IL-6, and resident macrophages in adipose tissue are capable of releasing TNFA. This normal phenotype of adipose tissue changes drastically with obesity. Firstly, obesity drives the enlargement of adipocytes (Gustafson, 2010). Enlarged adipocytes express markedly less adiponectin, thus promoting atherosclerosis. Enlarged adipocytes also release more PICs (including TNFA and IL-6) and release more free fatty acids than normal adipocytes, further promoting the development and progression of atherosclerosis.

1.3.3.4 AMI as caused by acute plaque disruption

After the formation of an atherosclerotic plaque, there are three principle ways it may be disrupted, all of which lead to the exposure of a highly thrombogenic surface to the blood, resulting in thrombosis, coronary occlusion, impaired oxygen delivery to the myocardium, and potentially myocardial infarction. The most common plaque disruption is a plaque rupture (J. L. Anderson & Morrow, 2017), causing approximately 60% of atherothromboses (Sakakura et al., 2013). This occurs when the thin fibrous cap of a plaque breaks, exposing its highly thrombogenic necrotic core composed of foam cells to the bloodstream. The next most common type of plaque disruption is an erosion, which causes approximately 30% of atherothromboses (Sakakura et al., 2013). Erosions have no evidence of plaque rupture; instead, the endothelium becomes eroded, leaving behind a thrombogenic surface of SMCs and collagen (Sakakura et al., 2013). The least common type of plaque disruption (2-7%) is a calcified nodule (Sakakura et al., 2013). Thrombosis occurs on a thrombogenic calcified nodule when it protrudes through a broken fibrous cap (Sakakura et al., 2013). Interestingly, the proportion of plaque ruptures causing AMIs are decreasing due to the widespread use of statins (J. L. Anderson & Morrow, 2017). This means that there is a growing proportion of plaque erosions and calcified nodules as the cause of acute atherothrombotic events (J. L. Anderson & Morrow, 2017).

Regardless of the mechanism, a full occlusion of the coronary artery will generally cause full thickness ischemia/infarction of the myocardium and is characterised by ST segment elevation on an ECG (STEMI) (J. L. Anderson & Morrow, 2017). A partial occlusion or a full occlusion with sufficient collateral blood supply will result in partial thickness ischemia/infarction of the myocardium and result in a non-ST segment elevated MI (NSTEMI) or unstable angina (J. L. Anderson & Morrow, 2017). The reason AMIs can cause ECG changes is because infarcted myocardium loses its ability to propagate an electrical impulse. As a result, the waves of

depolarisation and repolarisation must take alternative paths to avoid the non-conductive myocardium, resulting in altered ECG waveforms.

Impaired blood flow to the myocardium initially results in reversible ischemia (J. L. Anderson & Morrow, 2017). Generally, irreversible damage to the myocardium occurs after 30 minutes of occlusion, at which point the criteria for an MI is satisfied (Boersma et al., 2003). Following occlusion, the ischemic myocardium becomes necrotic, and complications such as left ventricular dysfunction, arrhythmias, and sudden cardiac death may occur (J. L. Anderson & Morrow, 2017).

1.3.4 Epidemiology of CVD

1.3.4.1 Prevalence and incidence

Cardiovascular disease (CVD) is the leading cause of death worldwide and in the United States (Santulli, 2013). Globally, CVD accounts for 16.7 million deaths per year, and is expected to rise to 25 million deaths per year in 2025 (Dahlöf, 2010). This translates to 30% of all deaths worldwide (excluding stroke, which accounts for an additional 10% of all deaths) (Santulli, 2013). Despite the large prevalence of disease, CVD death rates in developed countries are decreasing due to better preventative strategies and management of CVD (Dahlöf, 2010). This however means more people are living with CVD and as a result the burden of disease comes primarily from complications and morbidity and less so from mortality (Dahlöf, 2010).

The epidemiology of coronary heart disease (CHD) shows a similar trend to that of overall CVD. The Global Burden of Disease study ranked ischemic heart disease as the top global cause of mortality (Murray et al., 2012). CHD causes one in three deaths globally in people over 35 (Sanchis-Gomar et al., 2016). Better prevention and management of CVD has caused death rates from CHD continue to decrease in developed countries, however, in developing countries, the trend is reversed as death rates continue to rise (Boersma et al., 2003). Comparing the late 1960's to the late 1990's, CHD mortality in the US fell 63% for men and

60% for women (Sanchis-Gomar et al., 2016). Similarly, CHD mortality fell 32% for men and 30% for women in the European Union (EU) over the same period (Sanchis-Gomar et al., 2016). Alternatively, in developing countries (including China, India, Sub-Saharan Africa, Latin America, and the Middle East), CHD mortality is expected to rise from 9 million in 1990 to 19 million in 2020 (Sanchis-Gomar et al., 2016). This is thought to be caused by increased life expectancies, western diets, smoking, and social and economic changes (Sanchis-Gomar et al., 2016).

Similar to CHD, the incidence of AMI has decreased steadily in developed countries. The adjusted incidence rate of hospitalisation for AMI has dropped by 4% per year in the US every year since 1987 (J. L. Anderson & Morrow, 2017). Similarly, the age and sex adjusted incidence rates of AMIs in the US have decreased by 24% (274/100000 to 201/100000) between 1999 and 2008 (J. L. Anderson & Morrow, 2017). Despite this, estimates state that every 42 seconds an American will have an AMI (Sanchis-Gomar et al., 2016), and AMI rates continue to rise in developing nations, as incident AMI rates are roughly inversely proportional to the nation's total income (J. L. Anderson & Morrow, 2017).

1.3.4.2 Risk Factors

Many CVDs share the same aetiology and thus have similar risk factors (Dahlöf, 2010). Risk factors are classified into modifiable and non-modifiable. Modifiable risk factors include hypertension, smoking, abdominal obesity, abnormal lipids, hyperglycaemia, physical inactivity, stress, and a lack of dietary fruits and vegetables (Dahlöf, 2010). Non-modifiable risk factors include advanced age, male gender, genetic predisposition, and ethnicity (particularly high risk in South Asians) (Forouhi & Sattar, 2006). There is also an emerging body of evidence that inflammation is a risk factor for CVD, which was discussed previously in section 1.3.3.

More than 90% of AMIs are attributed to modifiable risk factors, as demonstrated by the INTERHEART global case-control study (Dahlöf, 2010). Similarly, an RCT enlisting people with

stable CHD and myocardial ischemia showed that intensive pharmacological therapy and lifestyle intervention resulted in the same amount of adverse cardiovascular events as people receiving PCI (18.5% and 19% respectively) (Boden et al., 2007). This highlights the importance of overall lifestyle modification in the prevention of AMI and CVD.

Risk factors for CVD tend to occur in clusters and not individually. Over 70% of those at risk of CVD have more than one risk factor (Dahlöf, 2010). These risk factors also act synergistically. People with no sub-optimal modifiable risk factors have a lifetime CHD risk is less than 5%, compared to a risk of 31-50% for those who have two or more suboptimal modifiable risk factors (J. L. Anderson & Morrow, 2017). Similarly, people with one risk factor are at a 4-fold increase of cardiovascular events, while people with five risk factors are at a staggering 60-fold increased risk (Dahlöf, 2010). Additionally, smaller optimisations of multiple risk factors result in a larger reduction in cardiovascular risk compared to larger reductions in a single risk factor (Dahlöf, 2010). For example, a modest 10% reduction in both systolic blood pressure and cholesterol translates into a 45% reduction in major CVD incidence (Dahlöf, 2010). Therefore, it is important to consider cardiovascular risk factors together and not in isolation of each other. This has prompted the development of global CVD risk scores, such as QRISK2. These scoring systems take into account multiple risk factors of CVD and produce a likelihood of having a cardiovascular event over a given time period. These scores are important because the majority of CVD events occur not in the high-risk population, but instead in those with low to moderate risk of disease (Dahlöf, 2010). Low to moderate risk individuals usually go unnoticed because many abnormal risk factors can be asymptomatic for many years, giving rise to the unfortunate scenario where the first manifestation of CVD may be death (Dahlöf, 2010).

The increasing prevalence of certain risk factors means that the prevalence of CVD will continue to rise in the future. In 2008, The Health Survey for England estimated that one in four adults in the UK were obese (defined as BMI >30 kg/m2) (Agha & Agha, 2017). Similarly, in

2010, it was estimated that 33% of men and 28% of women were obese, and this is expected to increase to 60% of men and 50% of women by 2050 (Agha & Agha, 2017). Similar trends have been seen in the US, where obesity rates have increased from 12% to 21% from 1991 to 2002 (Dahlöf, 2010). As obesity is a major risk factor for CVD, efforts in reducing CVD should start at interventions aimed at reducing BMI. Additionally, it is well known that hyperglycaemia and diabetes mellitus are strong risk factors for adverse coronary events. It was estimated by the American Heart Association in 2013 that 8.3% of adults in the US have diabetes mellitus and 38.2% of adults have prediabetes (Santulli, 2013). This represents a sharp increase from 1990 when there was an estimated 4.9% of adults with diabetes mellitus (Dahlöf, 2010), and may cause an increase in future CVD prevalence. Furthermore, 16.5% of all deaths in the world can be attributed to hypertension, as well as approximately half of all strokes and CHD related deaths (Santulli, 2013). Hypertension is the most important preventable cause of death worldwide, affecting 972 million in 2000, and estimated to rise to 1.6 billion in 2025 (Dahlöf, 2010). Hypertension is a strong risk factor for MI, heart failure, and stroke, however only half of all people in the US with hypertension have it controlled to an optimal level (Santulli, 2013).

1.3.5 Clinical Features

The cardinal symptom of an AMI is chest pain or discomfort. However, it is important to realise that AMI is not the only cause of cardiac chest pain. It is also important to consider a wide list of non-cardiac conditions that also cause chest pain or discomfort.

For any patient presenting with chest pain, the clinician must consider acute coronary syndrome (ACS) as a cause (Boersma et al., 2003). ACS encompasses three diseases, two of which are classified as myocardial infarctions (STEMI and NSTEMI), with the third being unstable angina. These three conditions can be distinguished from each other by ECG (only STEMIs have ST-segment elevation) and by measuring cardiac biomarkers such as cardiac

troponin (STEMIs and NSTEMIs have raised cardiac troponins, unstable angina does not) (Thygesen et al., 2019).

While stable angina causes pain that is relieved by rest, the pain of ACS is persistent and often lasts longer than 10 minutes (J. L. Anderson & Morrow, 2017). The classic description of the pain is a heavy retrosternal burning or pressure, however, it is important to note that pain may be felt in the shoulder, arm, jaw, epigastrium, or the back (J. L. Anderson & Morrow, 2017). The pain is diffuse and not specific and is not changed by movement or position (Thygesen et al., 2019). Importantly, up to 20% of ACS are silent (painless) or atypical (no significant pain) (J. L. Anderson & Morrow, 2017). These presentations are especially common in the elderly and in diabetic patients. As such, one cannot rely on chest pain alone to identify ACS. It is important to be able to recognise the associated features of AMI, including dyspnoea, diaphoresis, nausea and vomiting, fatigue, or unexplained weakness (Thygesen et al., 2019).

Clinical examination may reveal added heart sounds including S4 gallops or murmurs such as the one associated with mitral regurgitation. An anterior wall AMI may produce tachycardia or hypertension, while an inferior wall AMI may produce bradycardia or hypotension (J. L. Anderson & Morrow, 2017).

1.3.6 Management

1.3.6.1 General Care

All patients with suspected ACS are to undergo an immediate 12-lead ECG, whether in the community by paramedics or in hospital. This will help rule ACS in or out and differentiate myocardial infarctions from unstable angina (Boersma et al., 2003). Serial cardiac troponins are also performed to help confirm a diagnosis of AMI. A combination of the patient's history, clinical examination, ECG results, and cTn levels will determine whether the person has ACS, and if so, what management pathway will be employed (Boersma et al., 2003). General care for all patients with ACS include bed rest, Aspirin (75-325 mg), a second antiplatelet (often a

P2Y12 inhibitor), anticoagulation (often low molecular weight heparin), nitrates (for chest pain), oxygen (for hypoxemia), a high dose statin, morphine (for pain relief), a beta-blocker, and an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) (J. L. Anderson & Morrow, 2017).

Following general care, the patient is to undergo a specific management plan based on the presence or absence of a STEMI/NSTEMI and their immediate risk of adverse events, calculated by accredited risk scores such as GRACE (Global Registry of Acute Cardiac Events) or TIMI (thrombolysis in myocardial infarction).

1.3.6.2 STEMI Management

As described previously, a STEMI implies a full vessel blockage and full thickness myocardial ischemia and eventually infarction. Therefore, the patient should undergo coronary angiography (CA) and immediate coronary reperfusion through percutaneous coronary intervention (PCI) (J. L. Anderson & Morrow, 2017). This is the gold standard reperfusion strategy for hospitals capable of performing PCI within 90 minutes from medical contact and within 12 hours of first presentation (J. L. Anderson & Morrow, 2017). Patients in hospitals without the capacity to perform PCI and patients who cannot be transferred to a centre with PCI within 120 minutes from first medical contact should receive IV fibrinolytic therapy.

Studies have shown the benefits of PCI compared to fibrinolytic therapy. A review of 23 randomised trials in 2003 found that PCI was superior to intravenous thrombolytic therapy in reducing overall short-term mortality (27% reduction), stroke, non-fatal re-infarction, and a combined endpoint encompassing all three outcomes (Keeley et al., 2003). PCI also offers lower rates of intracranial haemorrhage (Boersma et al., 2003). While it used to be debated whether stenting or balloon angioplasty was preferred, it is now accepted that drug-eluting stents are the gold standard for PCI (J. L. Anderson & Morrow, 2017). Additionally, radial access (compared to femoral) has been shown to have a lower rate of access site bleeding,

major bleeding, and lower death rates, at the cost of a procedure time that is on average 2 minutes longer (J. L. Anderson & Morrow, 2017).

1.3.6.3 NSTEMI Management

NSTEMIs are different from STEMIs in that there remains residual perfusion within the ischemic zone due to partial occlusion of the coronary artery (J. L. Anderson & Morrow, 2017). Fibrinolytics are contraindicated in NSTEMIs due to the lack of therapeutic effect found in previous studies and their potential to cause harm (Daga et al., 2011). Therefore, the patient must be triaged into either an invasive (PCI) or ischemia guided (conservative) management plan (J. L. Anderson & Morrow, 2017). This is decided based on the risk of recurrent ischemia (determined by GRACE or TIMI risk scores), the services available at the hospital, and by the preference of the patient and doctor (J. L. Anderson & Morrow, 2017). High-risk patients and those with rising troponins or complications (including heart failure) are treated invasively with PCI, while low-risk patients receive conservative management.

1.3.6.4 Secondary prevention

Secondary prevention plans include diet and lifestyle advice and pharmacological therapy including aspirin, beta-blockers, ACEI or ARB, statins, and anticoagulants. These medications are taken long term to lower the risk of having a recurrent cardiovascular event.

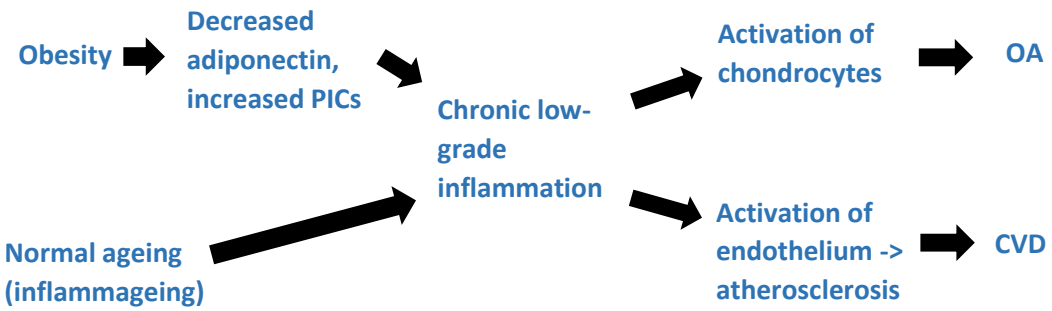
1.4 AMI and OA

The two previous sections have eluded to links between osteoarthritis and cardiovascular disease. These links stem from epidemiological studies showing associations between the two diseases and from research into a potentially shared pathophysiology. Links between OA and specifically AMI are unclear because of conflicting reports of associations. The following section will further outline the links between OA and AMI.

1.4.1 Associations between OA and AMI

There is an apparent lack of consensus regarding the association between OA and AMI. A 2013 cross-sectional study in Canada investigating the prevalence of CVD in people with OA found that OA was associated with AMI in women (OR 1.49, 95% CI 1.28 to 1.75) but not in men (OR 1.08, 95% CI 0.91 to 1.28) (Rahman, Kopec, Cibere, et al., 2013). Interestingly, the same study found that OA was significantly associated any heart disease in both men and women (OR 1.45 95% CI 1.36-1.54), even after adjustment for demographics and traditional CVD risk factors. A longitudinal study looking at the risk of CVD events in people with OA found that OA was associated with incident AMI in unadjusted models (OR 1.20, 1.09 to 1.32), however, the association became non-significant following adjustment for demographics and cardiovascular risk factors (AdjOR 1.02, 95% CI 0.92 to 1.12) (Rahman, Kopec, Anis, et al., 2013). The same study found that even after adjustment for demographics and traditional CVD risk factors, OA predicted CVD events (AdjOR 1.13, 95% CI 1.07 to 1.18). A systematic review and meta-analysis from 2017 looking at the association between AMI and various types of arthritis summarised that OA was associated with AMI after adjusting for age and sex (RR 1.31, 95% CI 1.01 to 1.71), however this effect became non-significant after traditional CVD risk factors were added as covariates to the model (Schieir et al., 2017). A prior systematic review and meta-analysis from 2016 looking at OA with various types of CVD found that OA was associated with heart failure (RR 2.8, 95% CI 2.25 to 3.49) and ischemic heart disease (RR 1.78, 95% CI 1.18 to 2.69), but not with MI or stroke (Hall et al., 2016). This suggests that OA may be associated with overall CVD, but associations between OA and AMI are still uncertain.

Figure 1.2: A proposed mechanism linking osteoarthritis and cardiovascular disease.



1.4.2 Shared Pathophysiology?

There are striking similarities between the risk factors of both OA and CVD. Two of the strongest risk factors for both diseases are advanced age and obesity. As discussed previously, there is an emerging body of evidence that inflammation plays a crucial role in the pathogenesis of both diseases. Given the roles that both advanced age and obesity have in creating an inflammatory state (via inflammageing and adipocytokine dysregulation), Figure 1.2 is a mechanism proposed by this author that could explain the link the pathophysiology of CVD and OA.

As discussed previously, obesity leads to a change in adipocyte phenotype. The new phenotype has a propensity to release greater amounts of inflammatory markers (such as TNFA and IL6) and fewer anti-inflammatory mediators (such as adiponectin). Additionally, inflammageing results in an increased level of pro-inflammatory mediators in the body. Both of these processes result in a chronic state of low-grade inflammation. An inflammatory environment is conducive to cardiovascular disease as it promotes the activation of vascular endothelium, the development and of atherosclerotic plaques, and the destabilisation of fibrous caps through the induced senescence of smooth muscle cells (which normally stabilise the fibrous cap by releasing extra-cellular matrix). Similarly, an inflammatory environment may increase the risk of OA through chondrocyte activation, resulting in the release of MMPs into the joint space, followed by degradation of the articular cartilage.

1.5 Systematic search to identify peer-reviewed papers that examine for the association between OA and management strategies and outcomes following AMI.

1.5.1 Introduction

Further research into the role that inflammation plays in both OA and CVD is required to help elucidate associations and shared pathophysiological mechanisms between these two prevalent and important diseases. While there have been strong reports of an association between OA and overall CVD, there is a lack of consensus on the association between OA and AMI. It is also unclear if OA is associated with poorer outcomes following AMI. This section describes a systematic review that was designed with the aim of identifying papers and synthesising the information in the published literature to determine whether OA was associated with the treatments offered or the outcomes following AMI. The best way to examine this association is through secondary care electronic health record data (EHR). This is because AMI is an acute event that is not managed in primary care. Additionally, survey designs are less appropriate because of the serious nature of AMI. Therefore, routinely collected electronic health record data from secondary care visits is the most likely study design to answer the research question of whether OA is associated with the receipt of invasive management strategies (coronary angiography, percutaneous coronary intervention, and CABG) and clinical outcomes (in-hospital mortality, major acute cardiovascular or cerebrovascular events, all-cause bleeding, and stroke/TIA) following AMI.

1.5.2 Systematic reviews

The two main types of research are primary and secondary studies (Jalali & Wohlin, 2012). Primary studies are novel and try to answer a specific research question. Secondary studies involve reviewing previous literature to provide a summary or overall opinion. Narrative reviews and systematic reviews are the two main ways that one can summarise a body of

literature. Narrative reviews are descriptive and often focus on a select few studies, as chosen by the author (Uman, 2011). Because there is no element of reproducibility or objectivity, narrative reviews may be subject to bias (Wright et al., 2007).

Systematic reviews allow researchers to answer specific research questions in a rigorous and reproducible manner. The methodology directs the identification of a vast amount of information about a topic; distillation of this into a palatable amount of information can inform clinical practice or policy making (Uman, 2011). Systematic reviews follow explicit methods, which include the formation of a research question, creating a search strategy, applying the search strategy in a database, screening the search results for relevant articles, and finally appraising and synthesising the information.

There are many benefits to systematic reviews. The synthesis of information from a number of studies, each with different settings, populations, and measurements of disease, means that conclusions are more generalisable than that of a single study (Rumona, 2014). Systematic reviews have explicit methods that help to limit bias and can be easily reproduced to validate findings. Articles can be arranged into a Forrest plot to provide a summary of the effect sizes of each study and to estimate the heterogeneity of the included studies. Systematic reviews also allow for meta-analysis, which is the pooling of data from individual studies into a larger sample that may be analysed as a whole. The increased sample size means an increased statistical power, which is important for rare events or when analysing small effect sizes (Biondi-Zoccai et al., 2011). Increased statistical power also narrows the range of confidence intervals allowing for more precise estimates. Perhaps most importantly, meta-analysis can uncover associations that may otherwise have been missed. A well-known example of this is a systematic review on the efficacy of corticosteroids in maturing the lungs of preterm infants, which identified 7 trials, of which only two demonstrated corticosteroids having a significant benefit (Roberts et al., 2017). However, by pooling the seven trials together and increasing the

sample size and power, it was discovered that corticosteroids did indeed have a statistically significant benefit to the lungs of premature babies. Important findings such as this may be missed without performing a meta-analysis.

There are some considerations when undertaking a systematic review. Firstly, a search that is not broad enough may miss relevant studies, however, a search that is too broad may be extremely time consuming. The search terms are also vital in the accuracy of the search and experienced researchers are required to ensure that it is performed correctly (Rumona, 2014). Additionally, a systematic search is only as valid as the studies that it synthesises. Finally, publication bias, the withholding of negative results from publication, is not accounted for in systematic searches.

1.5.3 The aims of this systematic review were:

1) To identify studies that have examined if OA is associated with the receipt of invasive management strategies (coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting) or adverse clinical outcomes (mortality, all-cause bleeding, major acute cardiovascular or cerebrovascular events, and stroke/TIA) following AMI, using electronic health record (EHR) data.
2) To synthesise data from relevant articles and establish if associations exist.

1.5.4 Methods

A systematic review protocol was first developed using the Arthritis Research UK Primary Care Centre Systematic Review Protocol & Support Template. This protocol included the proposed search terms and was approved by members of research staff before the search was performed. The search was executed using OVID Medline® (OVID Technologies Inc, 2019) to search the MEDLINE database from 1946 to the present (November 2019). To act as a sensitivity analysis for the first database search, a second search using EBSCOhost (EBSCO industries, 2020) was used to search all health databases, which included The Allied and

Complementary Medicine Database (AMED), MEDLINE, APA PsychInfo, APA PsychArticles the Cumulative Index of Nursing and Allied Health Literature (CINAHL), AgeLine, and SPORTDiscuss. These databases encompass all of the health databases that relevant research would be published in.

1.5.4.1 Search strategy

A comprehensive search strategy was developed to search for key words in both search engines. Keywords included all synonyms for osteoarthritis (osteoarthr* or OA or arthrit* or “joint pain”), AMI ("myocardial infarct*" or "MI" or "AMI" or "STEMI" or "NSTEMI" or "heart attack*”), and EHR ("medical record*" or "health record*" or "CPRD" or "clinical practice research datalink" or "CIPCA" or “nationwide inpatient sample” or NIS or "Consultations in Primary Care Archive" or computerised health record* or computerized health record* or electronic health record* or electronic medical record* or EHR or "electronic record*").

Because MEDLINE is indexed with Medical Subject Heading (MeSH) terms, these terms were also used in the OVID search. The MeSH terms for OA were divided by the site of OA, which were unspecified OA (osteoarthritis/), hip OA (osteoarthritis, hip/), knee OA (osteoarthritis, knee/), and spine OA (osteoarthritis, spine/). MeSH terms were also used for AMI (myocardial infarction/ or anterior wall myocardial infarction/ or inferior wall myocardial infarction/ or non-st elevated myocardial infarction/ or st elevated myocardial infarction/) and EHR (electronic health records/ or medical record systems, computerized/).

1.5.4.2 Eligibility criteria

The research question was designed using the PICO (population, intervention/exposure, control, and outcomes) framework. The population of interest was all adults diagnosed with an acute myocardial infarction in secondary care. Primary care studies were excluded because AMI is unlikely to be diagnosed or managed in the primary care setting, and secondary care is the most likely setting to capture patients diagnosed with and treated for AMI. The exposure

was a concurrent diagnosis of OA, and controls were people without a concurrent diagnosis of OA. Primary outcomes included procedures offered (such as the proportion receiving CA, PCI, and CABG) and outcomes (such as in-hospital mortality, cardiovascular and cerebrovascular complications, bleeding, and stroke or TIA). These primary outcomes were chosen because they are the most commonly performed treatments for and complications of AMI (White & Chew, 2008). Additionally, previous studies have used the same primary outcomes to determine the association of a concurrent diagnosis of cancer or mental illness on outcomes following AMI (Bharadwaj et al., 2019; Mohamed et al., 2019).

Inclusion criteria were a focus on the association between OA and outcomes following AMI, the use of electronic health record data, and the type of study design (cross-sectional, cohort studies, and systematic reviews). Studies were excluded if electronic health record data was not used, if patients were seen in primary care, or if patients were diagnosed with inflammatory arthritis. There were no exclusions for age of publication or language in which the paper was published.

1.5.4.3 Screening

The search results from both searches were imported into Mendeley where duplicate citations were removed. The results were title and abstract screened in Mendeley against the eligibility criteria by the author of this thesis. The articles that remained were screened by review of their full text. Remaining articles would be included for data extraction and synthesis.

A template was designed for data extraction; this would extract data on lead author name, year of publication, country, study type, study population, number of participants, mean age, percent female, clinical outcome measures, case definition of OA, case definition of AMI, main findings, and confounding variables adjusted for.

1.5.4.4 Critical appraisal and narrative synthesis

Articles that met the inclusion criteria would be critically appraised using validated tools from the Critical Appraisal Skills Programme (CASP) (Singh, 2013). These appraisal tools are designed to assess a studies internal validity, level of bias in the exposure and outcome variables, assessment of confounders, power, reproducibility, and external validity.

Whether a narrative synthesis or meta-analysis, or both, would have been performed was dependent on the number of studies identified and similarities between studies. A narrative synthesis can summarise the results of the identified studies. The eligible studies will be displayed on a Forrest plot, and should there be little heterogeneity between the studies, meta-analysis will be conducted. Meta-analysis involves combining the estimates of each study into a pooled estimate to provide a summary statistic for all included studies.

Alternatively, "vote-counting", which compared the sums of the positively and negatively associated studies, may be used to establish the overall direction of the relationship (Stewart, 2010).

1.5.5 Results

1.5.5.1 OVID Medline® Search

The systematic search of OVID Medline® identified 46 peer-reviewed papers which were imported into Mendeley (Table 1.1). There were no duplicate articles. Title and abstract screening excluded all 46 articles from being included within this review. Many articles were excluded because they investigated associations between OA and incident AMI and did not investigate outcomes following AMI.

Table 1.1: OVID Medline search results.

Search Number	Search Terms	Number of Results
1	osteoarthritis/ or osteoarthritis, hip/ or osteoarthritis, knee/ or osteoarthritis, spine/	60,611
2	(osteoarthr* or OA or arthrit* or "joint pain").mp.	273,888
3	1 or 2	273,888
4	myocardial infarction/ or anterior wall myocardial infarction/ or inferior wall myocardial infarction/ or non-st elevated myocardial infarction/ or st elevation myocardial infarction/	166,565
5	("myocardial infarct*" or "MI" or "AMI" or "STEMI" or "NSTEMI" or "heart attack*").mp	244,933
6	4 or 5	244,933
7	3 and 6	1421
8	medical records systems, computerized/ or electronic health records/	36,458

9	("medical record*" or "CPRD" or "clinical practice research datalink" or "CIPCA" or "Consultations in Primary Care Archive" or "nationwide inpatient sample" or NIS or computerised health record* or computerized health record* or electronic health record* or electronic medical record* or EHR or "health record*" or "electronic record*").mp	192,019
10	8 or 9	192,019
11	7 and 10	46

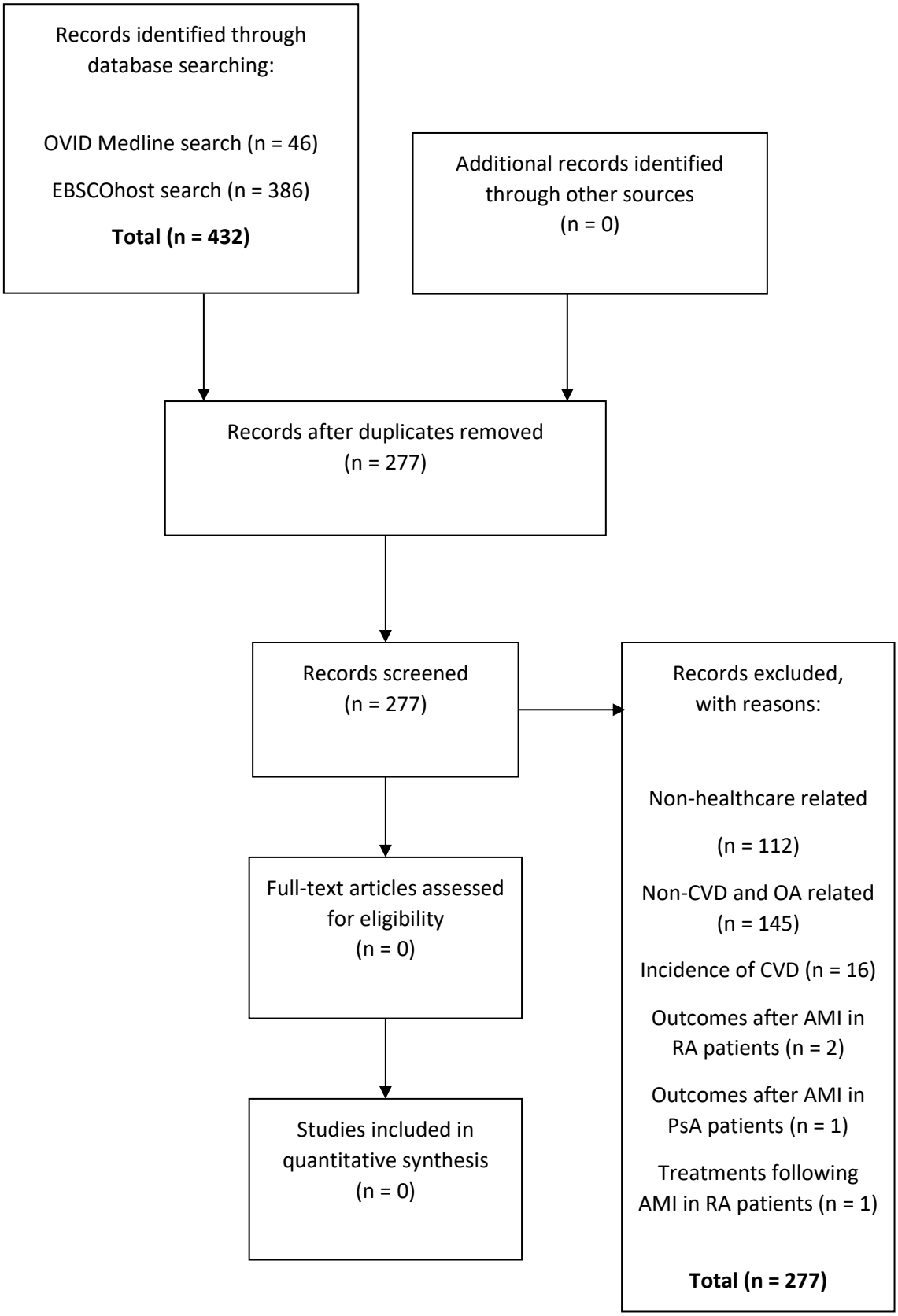
1.5.5.2 EBSCOhost search

The systematic search of EBSCOhost identified 386 articles (Table 1.2). Upon exporting the articles, 26 duplicate articles were removed by EBSCOhost. The remaining 360 articles were imported into Mendeley, where a further 95 duplicate articles were removed. All remaining 265 articles were title and abstract screened in Mendeley. None met the inclusion criteria. Many studies were excluded because they investigated inflammatory arthritis instead of osteoarthritis.

Table 1.2: EBSCOhost search results.

Search Number	Search Terms	Number of Results
1	osteoarth* OR “OA” OR “arthrit*” OR "joint pain"	505,689
2	myocardial infarct* OR “MI” OR “AMI” OR “STEMI” OR “NSTEMI” OR "heart attack*"	711,607
3	"medical record*" OR CPRD OR "clinical practice research datalink" OR "CIPCA" OR "Consultations in Primary Care Archive" OR "nationwide inpatient sample" OR *NIS* OR "computerised health record*" OR "computerized health record*" OR "electronic health record*" OR "electronic medical record*" OR "EHR" OR "health record*" OR "electronic record*"	577,223
4	1 and 2 and 3	386

Figure 1.3: PRISMA flow diagram.



1.5.6 Discussion

From the search of OVID databases, no articles were found that investigate the effect of OA on the management or outcomes following AMI. Acting as a sensitivity analysis, the second systematic search using EBSCOhost similarly found no relevant articles. As a result, there was no data available for extraction and a narrative synthesis and meta-analysis was not possible. Several articles were found to examine associations between OA or RA and incident CVD, however, no articles examined the prognostic effect of OA following AMI. One of the exclusion criteria of this review was studies set in primary care, however, none of the identified papers were excluded for this reason. Four articles met the inclusion criteria except for that they studied inflammatory arthritis. Two of these studies examined the effect of rheumatoid arthritis (RA) on mortality after AMI and found conflicting results (Francis et al., 2010; McCoy et al., 2013). The third study found that following PCI or CABG, RA patients experienced a lower mortality rate compared to people without RA (Varghese et al., 2010). The final study found that psoriatic arthritis had a protective effect on mortality following AMI (Jatwani et al., 2020). Moreover, no studies were found to examine the effect of OA on outcomes following AMI. This is surprising because previous literature has shown that people with OA are associated with activity limitations, decreased quality of life, and various comorbidities including cardiovascular diseases, peptic ulcer disease, and psychological diseases (Hunter et al., 2014; Swain et al., 2019; Vina & Kwoh, 2018). Research into the effect of OA after cardiovascular disease events seems a natural next step.

One strength of this search was the systematic approach used to identify relevant articles. Each search term was comprehensive and inclusive of all synonyms and was verified by an expert panel consisting of a senior lecturer in public health and epidemiology and a consultant cardiologist. Additionally, one can be confident that all major databases were searched. In particular, MEDLINE is a very comprehensive database that contains over 25 million references to journal articles in biomedicine and all of life sciences (MEDLINE®, 2019). MEDLINE records

are also indexed with Medical Subject Headings (MeSH), which help organise records to allow for a more efficient search (MEDLINE®, 2019). MEDLINE encompasses all key peer-reviewed cardiology and rheumatology journals. Therefore, one can be reasonably confident that this search was comprehensive.

Relevant papers may have been missed because the search terms were not inclusive enough. It is possible that relevant papers exist but were excluded because of the narrowness of the EHR search term. Additionally, this search would become more robust by using additional search interfaces. Finally, the review was undertaken a single reviewer. A second reviewer would help to ensure there was no bias in the screening process and may help uncover relevant articles.

1.5.7 Summary and further research

As previously highlighted, there are a number of studies that have identified an association between OA and overall CVD occurrence following adjustment for confounder. However, the association between OA and incident AMI is less clear, as there are conflicting reports of their relationship. The association between OA and the treatments and outcomes following AMI is unknown, as a systematic search of peer-reviewed papers investigating this relationship identified no eligible results. This gap in the literature will form the basis of this thesis and may help identify strategies to enhance the management of patients with OA who are diagnosed with AMI.

1.6 Thesis aims

The study described in the remainder of this thesis examines for whether there is an association between OA and the management and outcomes of people diagnosed with AMI. This work will be performed using the National Inpatient Sample (NIS), the largest inpatient secondary care database in the United States. from 2004 to 2015.

There were three aims for the study described in this thesis. Using NIS data, a sample representative to the entire US population, the first aim was to describe the prevalence of OA

in people with AMI for each year between 2004 and 2015. There have been no previous studies that have estimated the prevalence of OA in people diagnosed with AMI in a sample representative to the United States. It is hypothesised that the prevalence of OA in people with AMI will be higher than that of people without OA. It is also hypothesised that the prevalence of OA will increase over time due to better detection of OA and the increasing prevalence of its risk factors.

The second aim was to determine the strength and direction of the association between OA and various invasive management strategies following a diagnosis of AMI. The management strategies investigated were coronary angiography (CA), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). It was hypothesised that compared to people without a diagnosis of OA, people with OA were less likely to be offered invasive management strategies following AMI because of previous reports of comorbidity being associated with a decreased odds of coronary revascularisation (Haglund et al., 2004; Pathak & Strom, 2008).

The third aim was to determine the strength and direction of the association between a concurrent OA diagnosis and adverse clinical outcomes following a diagnosis of AMI. The clinical outcomes to be investigated are in-hospital mortality, major acute cardiovascular and cerebrovascular events (MACCE), all-cause bleeding, and acute stroke or TIA. It is hypothesised that compared to people without a diagnosis of OA, people with OA are more likely to experience adverse clinical outcomes following AMI. This is because people with OA are generally unhealthier than people without OA and OA is associated with many comorbidities including CVD, metabolic disease, and peptic ulcer disease (Swain et al., 2019).

2 Chapter 2: Methods

2.1 Introduction

The aims of this study were to describe the prevalence of OA in people admitted to secondary care for AMI for each year between 2004 and 2015 and to determine the strength and direction of the association between OA and invasive managements and outcomes following AMI. Secondary care data from the National Inpatient Sample (NIS), the largest inpatient electronic health record database in the United States (US), was used in this study. This chapter introduces the US healthcare system and describes electronic health record databases like the NIS. This chapter also discusses the variables used in this study and describes the statistical analysis that was performed.

2.2 The United States healthcare system

The United States, unlike many developed nations, does not have a universal healthcare system. Instead, Americans receive healthcare through a combination of public programmes such as Medicare and Medicaid (each of which having its own eligibility criteria) and private programmes paid for independently or by a person's employer.

Medicare was enacted in 1965 as part of the Social Security Act. It is paid for via tax revenue and provides basic primary and secondary healthcare to Americans over the age of 65 and people under 65 who have certain disabilities (Rowland & Lyons, 1996). While providing basic coverage, Medicare is not all-inclusive, with many medical conditions and procedures not being covered. Additionally, Medicare is not free at the point of contact. Beneficiaries of Medicare must pay monthly premiums, annual deductibles, and part of the cost of the health services they receive (called coinsurance) (Gornick et al., 1985).

Medicaid was also enacted in 1965 under the Social Security Act. Also paid for through tax revenue, Medicaid is available to specific low-income families and individuals of any age

(Rowland & Lyons, 1996). People enrolled in federal welfare payment programmes are automatically eligible for Medicaid (Gornick et al., 1985). Medicaid is also available to Americans who may end up relying on welfare programmes because of the cost of medical bills (Gornick et al., 1985). Additionally, Medicaid is essential in helping cover healthcare costs in low income elderly people for which Medicare is not entirely sufficient (Rowland & Lyons, 1996).

Americans who are not eligible for Medicare or Medicaid must pay for medical expenses through private health insurance plans or by paying of pocket. Because healthcare is not free at the point of contact, US hospitals accurately code all services they provide to patients in order to be appropriately reimbursed. This routinely collected billing information can be used for healthcare research and is the basis of many electronic health record databases, including the NIS.

2.3 Electronic health record data

Electronic health record (EHR) data is data that is routinely collected by healthcare providers or insurers often for billing purposes (Jorm, 2015). In addition to providing clinicians with essential information to help make decisions and provide safer care, EHR data may also be used to facilitate high quality medical research (Casey et al., 2016).

The use of EHR in medical research has many benefits. EHR data contains important routinely collected patient information including demographics, vital status, diagnoses, symptoms, medications, vaccinations, laboratory tests, referral letters, and specialist care information. Because EHR data can provide information on entire populations, it can be used as a tool for public health surveillance for communicable and chronic illnesses (Calman et al., 2012). The inclusion of a large population also facilitates the study of rare diseases or minority groups (Jorm, 2015). EHR data can be used for many study designs. If data is pseudo-anonymised (each record contains a nonidentifiable code that can be used to retroactively identify

participants), then individuals can be tracked over time and EHR data can be used for longitudinal designs such as cohort studies. Pseudo-anonymised data can also be linked to medical records for a more complete picture of a person's health status. When data is completely anonymised, longitudinal analysis is not possible and other designs (such as cross-sectional) must be used instead. Additionally, studies using EHR data are cheaper than surveys and may limit non-response bias, reporting bias, and attrition (Casey et al., 2016; Jorm, 2015).

There are also some important limitations when using EHR data in medical research. Firstly, coding is a potential source of error through either misclassification or non-random missing data (Hemingway et al., 2018). Diseases with well-defined criteria such as AMI are less likely to suffer from coding errors. However, diseases with many phenotypes and classifications (such as OA) rely more heavily on the judgement of the healthcare provider with respect to the accuracy of codes (Hemingway et al., 2018). Additionally, EHR data can be poor for conditions that are mild or remittent as people may not always seek medical attention (Casey et al., 2016). This is the case with OA, as people can live with the disease for many years before becoming symptomatic and seeing a primary care physician. These factors may make OA codes in EHR data less reliable and more error prone. Finally, EHR data may not capture important information that is not routinely collected, including diet, physical activity, employment status, socioeconomic status, smoking status, height and weight, and psychosocial factors (Casey et al., 2016).

Primary care EHR databases are commonly used for medical research in the UK. The Consultations in Primary Care Archive (CiPCA) is a pseudo-anonymised primary care EHR database based in North Staffordshire, and the Clinical Practice Research Datalink (CPRD) is a similarly pseudo-anonymised primary care EHR database that spans across the UK. In the United states, the technological advancement of the healthcare industry has lagged behind nearly every other major industry (Menachemi & Collum, 2011). This prompted the Health

Information Technology for Economic and Clinical Health (HITECH) act of 2009, which incentivised healthcare providers to adopt EHR systems (Menachemi & Collum, 2011). The largest secondary care EHR database in the United States is the National Inpatient Sample (NIS), which is the data source for this study.

2.4 The National Inpatient Sample (NIS)

2.4.1 Overview

The NIS is a routinely collected administrative discharge database developed by the Agency for Healthcare Research and Quality (AHRQ) and contains data on approximately 7 million hospital admissions in the US per year (Healthcare Cost and Utilisation Project, 2019). The NIS is one of many databases developed for the Healthcare Cost and Utilisation Project (HCUP), which aimed to provide estimates of inpatient outcomes, access, quality, and costs across the United States. The NIS is the largest inpatient database in the US and the 2017 weighted sample is estimated to be representative to 97% of all discharges from community hospitals regardless of payer (including Medicare, Medicaid, private insurance, and uninsured). The AHRQ releases the NIS annually, with the dataset encompassing discharges from two years prior to the date of release. The 1988 NIS was the first version and the most recent version is the 2017 dataset, which includes 7,159,694 unweighted discharges from 4,584 hospitals across 48 states. The purchase of consecutive datasets allows for trend analysis across multiple years.

2.4.2 Data

The NIS includes both clinical and non-clinical information that comes from discharge summaries created by hospitals for billing purposes (Hertzer, 2012). The discharge summaries are created by trained coders who analyse inpatient medical records and assign the relevant codes to capture a patient's diagnoses, procedures, and other services that the hospital bills to the patient (Hertzer, 2012).

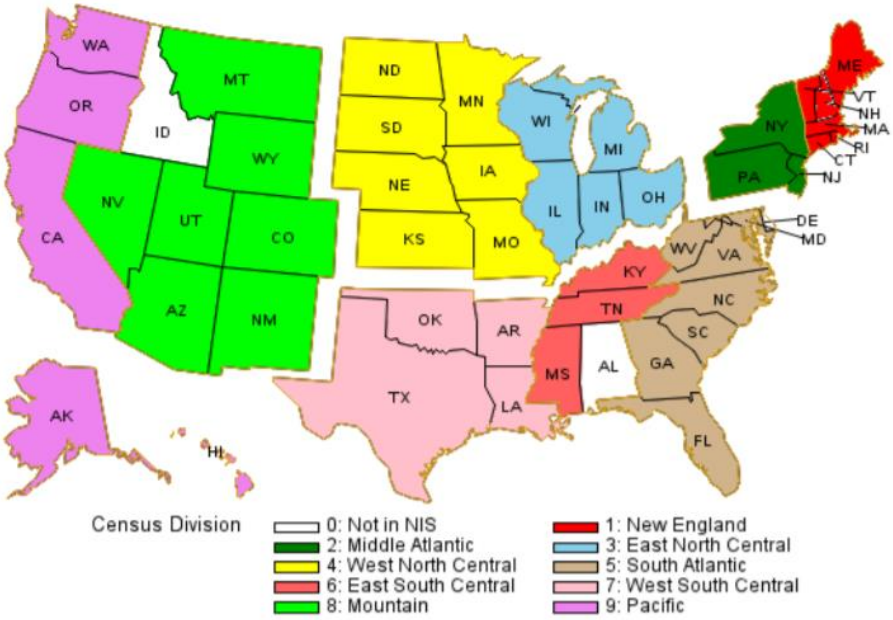
The information recorded in the discharge summaries (and subsequently in the NIS) includes 1 primary diagnosis code, up to 29 secondary diagnosis codes, and up to 15 procedure codes. Additional data elements include patient demographics (sex, age, race, and household income), length of stay, discharge status, total charges, and hospital characteristics.

Prior to October 1st, 2015, the NIS was coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). However, from the 1st October 2015 onwards, the codes used by the NIS changed to the newer International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS).

2.4.3 Sampling Method and Weights

The sampling frame of the NIS is every hospital admission in the US per year (approximately 35 million). Prior to 2012, the NIS was comprised of 100% of discharges from a sample of 20% of all eligible hospitals in the US, therefore representing a 20% sample of the population (Healthcare Cost and Utilisation Project, 2019). Weights were applied to each record in the 20% sample to allow for representative national estimates (for example, the 2015 NIS included 7,153,989 unweighted discharges and 35,769,942 weighted discharges). Weights were calculated by dividing the number of expected hospital admissions by the number of sampled hospital admissions within a stratum (Healthcare Cost and Utilisation Project, 2017). Strata are defined by hospital characteristics including census region (Figure 2.1), urban/rural location, bed size, teaching status, and ownership. The expected number of hospital admissions within a strata were estimated using the American Hospital Association annual survey. All patients admitted to hospitals with the same aforementioned characteristics will therefore have the same weight applied to them to produce national estimates.

Figure 2.1: The 9 census divisions used in the NIS from 2012 onwards. These divisions make up the 4 regions (used prior to 2012) as follows: Region 1 (Northeast) includes Divisions 1 and 2, Region 2 (Midwest) includes Divisions 3 and 4, Region 3 (South) includes Divisions 5, 6, and 7, and Region 4 (West) includes Divisions 8 and 9 (Healthcare Cost and Utilisation Project, 2014).



2.4.4 2012 Redesign

In 2012, the NIS changed name from the "Nationwide Inpatient Sample" to the "National Inpatient sample" and underwent a redesign in order to reduce sampling error, improve confidentiality, and produce better national estimates (Healthcare Cost and Utilisation Project, 2014).

Starting in 2012, the NIS changed its sampling method. Instead of taking 100% of discharges from a sample of 20% of all eligible US hospitals, the NIS is now comprised of a 20% sample of all discharges from all hospitals in the US. The sample size of the NIS remained 20% of the sampling frame. Prior to 2012, the NIS divided the US into 4 census regions, which were Northeast, Midwest, South, and West. The new sampling method divides the US into 9 census divisions, which are New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific (Figure 2.1). All

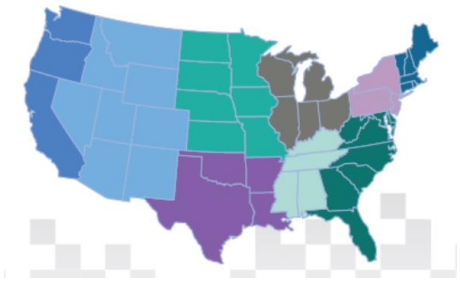
discharges within a division were ordered by hospital. Every hospital's discharges within a division were then ordered by diagnosis-related groups (DRG) (every patient is assigned to one of over 700 DRGs, with each group having similar illnesses and in-hospital care). The list of hospital discharges is also ordered by admission month. This ordered list of hospital discharges was then sampled such that every fifth discharge is chosen, thus producing a 20% sample of the sampling frame (Figure 2.2). Weights were then calculated for each hospital admission in the same way as prior to the redesign (except that census division replaces census region when defining a hospital strata). This new sampling method was performed for every hospital in all 9 census divisions. Ordering by DRGs and admission month ensured that the sample was representative with respect to these two patient factors. Similarly, sampling from all hospitals ensured representativeness to hospital level factors including census division, urban/rural hospitals, and teaching status. According to the redesign report, this new sampling strategy reduced sampling error and decreased confidence intervals for many estimates (Healthcare Cost and Utilisation Project, 2014).

The redesign also removed state and hospital identifiers from the discharges in order to enhance confidentiality. The lack of patient identifiers means that there is no way to track individual people within the NIS, as one person may contribute to multiple discharges in the dataset.

Additionally, the redesign saw the removal of long-term acute care hospitals from the dataset. Long-term acute care (LTAC) hospitals are defined as accredited acute care hospitals with an average length of stay greater than 25 days. The NIS removed LTAC hospitals because of a lack of uniformly available data across the participating states. The redesign report by HCUP stated that the effects of removing LTAC hospitals on estimates were minimal. Rehabilitation facilities have been excluded from the NIS since its inception.

Overall, this redesign has helped improve the NIS by reducing sampling error, improving confidentiality, and producing better national estimates. However this has come at the expense of worse hospital-to-hospital estimates, as the NIS no longer samples entire hospitals, but instead individual discharges (Khera & Krumholz, 2017).

Figure 2.2: A diagram illustrating the sampling method of the NIS

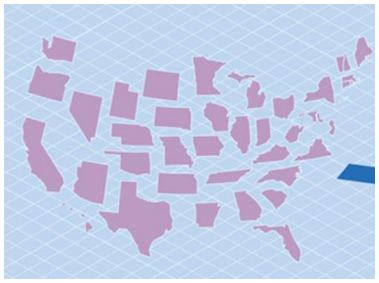


Sampling Frame:

All hospital admissions in the United States.

Sampling Method:

Hospital admissions are ordered by DRG and admission month, and every 5^{th} admission is sampled.



Sample Unit:

20% of all US hospital admissions make up the sampling unit.

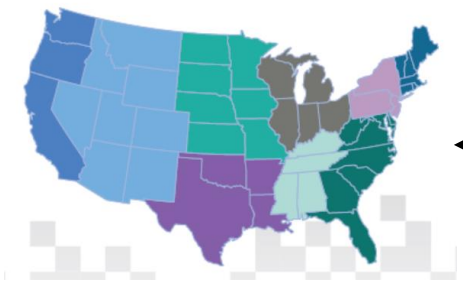
DISCWT

Discharge Weights:

Weights were calculated and applied to the sample unit using the equation:

$\frac{Expected\ admissions}{Sampled\ admissions}$ for each strata.

Strata were defined as having the same census region, urban/rural status, number of hospital beds, teaching status, and ownership.



Weighted Sample:

A nationally representative weighted sample of US hospital admissions.

2.5 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)

The ICD-9-CM is the official diagnosis and procedure classification system for US hospitals and is used by the NIS for all datasets prior to the 2016 version (Centers for Disease Control and Prevention, 2015). It is based on the World Health Organisations Ninth Revision, International Classification of Diseases (ICD-9). Two US government agencies, the National Centre for Health Statistics and the Centres for Medicare and Medicaid services, created the ICD-9-CM for use in the United States.

The ICD-9-CM consists of approximately 13,000 codes in 17 chapters (Cartwright, 2013). Volume 1 contains a tabular index of all disease codes grouped by body system, volume 2 contains an alphabetical index of all disease codes, and volume 3 contains codes for surgical, diagnostic, and therapeutic procedures. Codes may have a minimum of three and a maximum of five characters, in the style "XXX.XX" (Cartwright, 2013). The first three digits represent the body system and disease (Centers for Disease Control and Prevention, 2015). The final two digits represent the aetiology, anatomical site, and/or manifestation of the disease (Cartwright, 2013). Nearly all codes are entirely numeric. The exception are codes for factors influencing healthcare, external causes of injury, and the morphology of neoplasms, which start with the letters "V", "E", and "M", respectively, followed by a sequence of numbers (Cartwright, 2013).

2.6 Internal validity of EHR studies

Studies with high internal validity generate valid inferences and accurately measure the intended variables (exposures and outcomes) (Grimes & Schulz, 2002). Three ways that a study's internal validity can be negatively affected are through random error, systematic error,

and confounding (Tripepi et al., 2010). Random error can only be minimised by increasing the sample size of a study. Systematic error (or systematic bias) represents a flaw in a study's methodology and can potentially invalidate the findings. Confounding is a distortion of the true relationship between an exposure and an outcome due to a third (confounding) variable (Grimes & Schulz, 2002). Two important systematic biases to consider are selection bias and information bias (Grimes & Schulz, 2002).

2.6.1 Selection bias

Selection bias occurs due to differences between study participants and non-participants in variables besides the exposure of interest (Tripepi et al., 2010). Ideally, when comparing the cases versus controls and the participants versus non-participants, the groups will be similar in all respects except for the exposure of interest. There are many types of selection bias, some of which are not applicable to this study design. Non-response bias, loss to follow up bias, and volunteer bias are not applicable because the NIS uses routinely collected data from inpatient visits. Confounding by indication is also not applicable because this study's exposure is not a treatment that can be allocated.

2.6.2 Information bias

Information bias occurs following inaccurate measurement of the exposure or the outcome. Misclassification bias is the inaccurate assignment of either the exposure or the outcome such that exposed individuals are classified as non-exposed or diseased individuals are classified as non-diseased, or vice versa (Tripepi et al., 2010). There are two types of misclassification bias, non-differential and differential. In non-differential misclassification, the degree of misclassification of the exposure or the outcome is the same between cases and controls; differential misclassification bias is where the misclassification differs between cases and controls (Tripepi et al., 2010). Differential misclassification bias tends to skew estimate (odds ratios or relative risks) towards the direction of the bias, while non-differential

misclassification bias tends to skew estimates towards the null value (Grimes & Schulz, 2002). Information bias due to misclassification is inherent to all EHR databases, including the NIS (Hertzer, 2012).

2.6.3 Confounding

A confounder distorts the relationship between the exposure and the outcome by being associated with both variables without being on the causal pathway. Confounders can be adjusted for by being included as covariates in multivariable models. Unmeasured confounding is the omission of a relevant confounder from the model, while residual confounding is caused by measurement error of a confounder in the model (Fewell et al., 2007). Positive confounding is when a confounding variable leads to an overestimation of the true effect, resulting in adjusted analysis to have a smaller effect size than the unadjusted analysis (Mehio-Sibai et al., 2005). Negative confounding is when a confounding variable leads to an underestimation of the true effect, resulting in adjusted analysis to have a larger effect size than an unadjusted analysis. Positive confounders are associated in the same way (direct or inverse) to both the exposure and outcome (Szklo & Nieto, 2004). Negative confounders are differently associated with the exposure and outcome. For example, if a negative confounder is associated with an increased probability of the exposure (direct association), then the negative confounder should also be associated with a decreased probability of the outcome (inverse association) (Szklo & Nieto, 2004).

The variables that were considered to confound the relationship between OA and the management and outcomes following AMI were considered in the following section. The following section also contains a description of how the OA, invasive management, and adverse outcome variables were created.

2.7 Definitions of variables in this study

All variables in this study were derived by searching the NIS 2004 to 2015 data set for the relevant ICD-9-CM codes. The codes used for each variable were based on previous studies. A table of all codes is found in Appendix 6.1.

2.7.1 Acute myocardial infarction

This study's sample is comprised of people admitted to hospital for AMI between 2004 and 2015. These patients were identified by searching for ICD-9-CM codes for AMI in the primary diagnosis position. The parent ICD-9-CM code for AMI is 410.xx, where each "xx" can take any value to represent a daughter code for AMI. The specific codes for ST-elevated myocardial infarction include 410.0x for anterolateral, 410.1x for anterior, 410.2x for inferolateral, 410.3x for inferoposterior, 410.4x for inferior, 410.5x for lateral, 410.6x for posterior, 410.8x for other specified sites, and 410.9x for unspecified site (Bharadwaj et al., 2019). The codes for non ST-elevated myocardial infarctions were 410.7x (Bharadwaj et al., 2019). These codes were used to create a binary AMI variable.

2.7.2 Independent variable – osteoarthritis

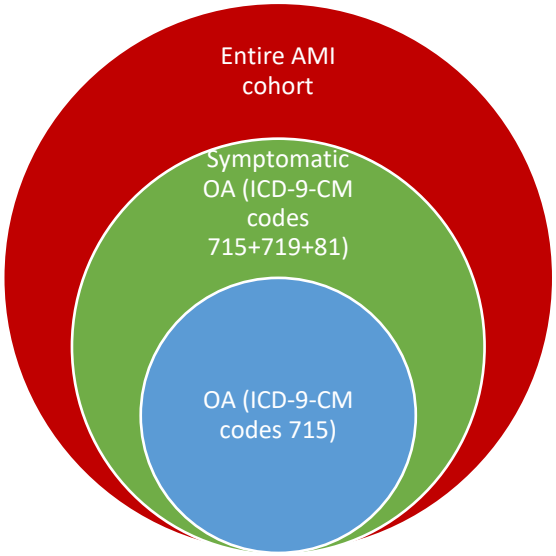
2.7.2.1 OA

After selecting for all people with a code for AMI in the primary diagnosis position, people with an additional ICD-9-CM code for OA were identified. ICD-9-CM codes 715.0x and 715.8x coded for generalised OA; 715.11-4, 715.21-4, 715.31-4, and 715.91-4 for upper limb OA; 715.15-7, 715.25-7, 715.35-7, and 715.95-7 for lower limb OA; 715.10, 715.18, 715.20, 715.28, 715.30, 715.38, 715.90, 715.98, and V134 for unspecified OA (Centers for Disease Control and Prevention, 2015). People were classified as having OA if an OA code was found in any of the 29 secondary diagnosis positions, thus creating a binary OA variable.

2.7.2.2 Symptomatic OA

Additionally, a binary "symptomatic OA" variable was created to perform a sensitivity analysis of the OA variable. Previous studies have highlighted the underreporting of OA in electronic health record databases (Yu et al., 2018). In particular, this study's definition of OA (ICD-9-CM 715.xx codes) has been shown to have a low sensitivity (34.6%) and low PPV (33.5%) (Cisternas et al., 2016). In order to overcome this, the symptomatic OA variable included the previously described OA definition (ICD-9-CM codes 715.xx) plus ICD-9-CM codes for pain in joint (719.4x) and effusion of joint (719.0x) in people over 50 years-old (key symptoms for OA) and ICD-9-CM codes for joint replacement. The age restriction was used because previous studies have suggested that an adequate definition of clinical OA is chronic pain in older adults, and people with additional radiographic changes are merely a subset of these patients (Thomas et al., 2004). The symptomatic OA definition also includes ICD-9-CM codes for joint replacement because OA is the most common indication for many joint replacement surgeries including total hip replacement (91.7%), total knee replacement (97.4%), and total shoulder replacement (92.7%) (National Joint Registry, 2019). Previous studies have identified patients undergoing joint replacement as an appropriate way to perform sensitivity analyses on definitions of OA (Yu et al., 2018). Joint replacement codes included in the "symptomatic OA" definition include total shoulder arthroplasty (81.80), shoulder hemiarthroplasty (81.81), reverse total shoulder arthroplasty (81.88), total hip arthroplasty (81.51), total knee arthroplasty (81.54), total ankle arthroplasty (81.56), ankle fusion (81.11), ankle arthrodesis (81.12), and total elbow arthroplasty (81.84) (Young et al., 2018). In summary, the symptomatic OA variable will act as a sensitivity analysis for the OA variable and will examine for the potential extent of information bias in this study's definition of OA.

Figure 2.3: Visual representation of the OA and symptomatic OA variables.



2.7.3 Dependent variables

2.7.3.1 Invasive management strategies

ICD-9-CM codes were used to create binary variables for the following invasive management strategies: coronary angiography (88.52, 88.53, 88.54, 88.55, 88.56, 37.22, and 37.23), percutaneous coronary intervention (00.66, 36.01, 36.02, 36.06, 36.07, and 36.09), and coronary artery bypass grafting (36.1×, 36.20, 36.31, 36.32, and 36.9×) (Bharadwaj et al., 2019).

These variables were chosen because they represent explicit management strategies for AMI and were likely to be well-coded compared to other conservative management strategies. Additionally, the NIS does not have information on pharmacological management, therefore interventional and surgical management strategies were the natural choice. Finally, these invasive management strategies have been used in previous studies that have examined AMI in the NIS (Bharadwaj et al., 2019; Mohamed et al., 2019).

2.7.3.2 Clinical outcomes

Four binary clinical outcomes were considered: in-hospital mortality, major acute cardiovascular and cerebrovascular events (MACCE), all-cause bleeding, and stroke or TIA. MACCE is a binary composite score that encompasses in-hospital mortality, cardiac complications, and stroke. Cardiac complications were defined as haemopericardium (423.0), cardiac tamponade (423.3), pericardiocentesis (37.0), or coronary dissection (414.12) (Bharadwaj et al., 2019). A variable representing all-cause bleeding was defined as gastrointestinal haemorrhage (578.0, 578.1, and 578.9) or intracranial haemorrhage (430, 431, and 432.x). Codes for stroke included 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, and 436 (Bharadwaj et al., 2019). In-hospital mortality, MACCE, all-cause bleeding, and stroke or TIA all represent hard endpoints that are likely to be well-coded in the NIS. These outcomes have also been used in previous studies of AMI in the NIS (Bharadwaj et al., 2019; Mohamed et al., 2019).

2.7.4 Confounding variables

As outlined above, the following confounding variables were selected because they may be (i) associated with osteoarthritis, (ii) associated with management strategies or outcomes and (iii) may explain the association between osteoarthritis and management strategies or outcomes following AMI.

2.7.4.1 Demographics

Patient demographic variables that were included in the NIS dataset are age (continuous), sex (binary), income quartile based on ZIP code (categorical), and payer (Medicare, Medicaid, private insurance, self-pay, no charge, or other). Hospital demographics include bed size (small, medium, and large), hospital region (Figure 2.1), and year of admission. Hospital region was used instead of hospital division because hospitals were only assigned divisions in the NIS from 2012 onwards. Additionally, a binary smoking history variable was created using ICD-9-CM codes V15.82 and 305.1 (Mohamed et al., 2019).

2.7.4.2 Past Medical history

A history of cardiovascular disease is associated with OA and an increased risk of recurrent cardiovascular events and death, which may confound the relationship between OA and outcomes following AMI (Govender et al., 2019; Rahman, Kopec, Cibere, et al., 2013). Therefore, previous cardiovascular disease and previous cardiovascular procedures were included as confounders. Specifically, binary confounding variables were created for a history of ischemic heart disease (IHD) (414.00-07, 414.2-9), previous AMI (412.xx), previous PCI (V45.82), previous CABG (V45.81), and previous stroke (V12.54) (Mohamed et al., 2019).

2.7.4.3 Comorbidities

The NIS comes with comorbidity data that is developed by the ARHQ and created by searching the ICD-9-CM codes and DRG's of each admission to create a binary variable for each comorbidity (Healthcare Cost and Utilisation Project, 2017). The comorbidities include acquired immune deficiency syndrome (AIDS), alcoholism, anaemia, rheumatological conditions, heart failure, chronic lung disease, coagulopathies, diabetes, depression, substance misuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological conditions, obesity, paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, renal failure, solid tumours with no metastasis, peptic ulcer disease, valvular heart disease, weight loss, and dementia. Previous studies of AMI in the NIS have included all comorbidity variables as covariates in logistic regression models (Bharadwaj et al., 2019; Mohamed et al., 2019). This study used all comorbidity variables except for "rheumatological conditions" because of potential co-occurrence and collinearity with it and the OA variable.

2.8 Analysis

2.8.1 Overview

This study focused on examining the association between binary exposures and outcomes. When both the explanatory variable (X) and the response variable (Y) are continuous and linearly related, the linear regression model $Y = a + BX$ is the simplest method of describing their relationship (Bender & Grouven, 1997). However, this model is only valid when Y can take any value from negative infinity to positive infinity. In situations where Y is binary, for example when measuring vital status (dead or alive) or the receipt of a treatment (0 or 1), the linear regression model is invalid. Logistic regression overcomes this by transforming the binary outcome Y (from only taking values of 0 or 1) into the logarithm of the odds of the outcome Y, which can be any real number.

Start with the binary outcome Y which can only take the value of 0 or 1. If p is the probability of the outcome Y=1, then p can be any real number between 0 and 1. Similarly, the odds of the event Y=1, described as the ratio of the probability of the event to the probability of the complement, or $\frac{p}{1-p}$, can hold any positive value. Finally, the natural logarithm of this odds, $\ln\frac{p}{1-p}$, can hold any value from negative infinity to positive infinity. This logarithm of the odds, also known as a logit, overcomes the previously violated assumption of a linear relationship between X and Y (Tu, 1996). As such, we can reapply the linear relationship to produce the equation $\ln\frac{p}{1-p} = a + BX$ (Tu, 1996). If we wish to model the probability of the event using multiple explanatory variables, we may add them to the equation as such: $\ln\frac{p}{1-p} = a +$ - $B_1X_1 + B_2X_2 + \cdots + B_nX_n$, where n is any positive integer (Bender & Grouven, 1997).

Using a process called maximum likelihood estimation, logistic regression finds the combination of B-coefficients that correspond to the highest likelihood of observing the

outcome (Stoltzfus, 2011). This process may involve many iterations to find this optimal combination of coefficients.

Because the logit equation describes the natural logarithm of the odds of an event, it follows that the exponent of a single B-coefficient will produce an unadjusted odds ratio (OR). In a multivariable model, the exponent of a single B-coefficient produces an OR that is adjusted for all the other variables in the model. Furthermore, this adjusted OR represents the effect that the exposure variable has on the outcome variable when all other covariates are held constant. Odds ratios greater than 1 indicate an increased odds of the outcome Y, while OR's less than 1 indicate a decreased odds. An OR equal to 1 indicates that there is no increased or decreased odds of the outcome and is called the null value.

The interpretation of this OR depends on the scale of measurement of the explanatory variable X, which may be continuous or categorical. Consider the example where a logistic regression model predicts a binary outcome (Y=0, or Y=1) from one binary (X_1) and one continuous (X_2) explanatory variable. Suppose the exponential of the B-coefficients produced an OR of 4.0 for X_1 and 2.0 for X_2. Because X_1 is binary, the interpretation of this result is "the odds of outcome Y is increased by 4-fold as X_1 "increases" from its reference value to its alternative value". Alternatively, because X_2 is continuous, this may be interpreted as "the odds of outcome Y is increased by 2-fold for every single unit increase in X_2". Furthermore, because there are two covariates in the model, the corresponding OR's are adjusted for each other (and any other explanatory variables in the model).

2.8.2 Considerations

There are many benefits to logistic regression. Firstly, the ability to examine multiple independent covariates at once allows researchers to easily control for confounding variables (Stoltzfus, 2011).

Another benefit of logistic regression is the ease in which it can be interpreted. Simply taking the exponential of a single coefficient will produce an OR that can be easily understood and interpreted.

The next important consideration is deciding which variables to include in the model. Covariates should be justified clinically or statistically (Stoltzfus, 2011). Too many variables may result in decreased generalisability and overfitting. A general rule is that there should be at least 10 cases belonging to each category of the binary dependent variable Y for every covariate in the model (Stoltzfus, 2011). Additionally, it is important to avoid multicollinearity by avoiding adjustment for the same variable twice (Stoltzfus, 2011). Multicollinearity results in large standard errors for beta coefficients. An example of collinearity is a model that adjusts for both weight and body mass index (BMI).

Model building strategies are the final consideration. There are generally three strategies (Stoltzfus, 2011). The first is the direct approach, which involves putting all covariates into the model at once with no assumptions about the relative strengths of the covariates. This method is best if researchers have no clear predetermined hypothesis. The second strategy is the sequential strategy, where you first add the covariate with the strongest association with the outcome, and then you continually add other covariates to the model one at a time. The final strategy is the stepwise strategy and uses a predefined selection criterion to choose covariates. An example of this is backwards elimination, where all covariates are placed into the model, and the nonsignificant covariates are removed one at a time until only covariates significantly associated with the outcome remain.

2.9 Statistical Analysis

2.9.1 Data cleaning

The NIS data from each year between 2004 and 2015, inclusive, was imported into IBM's Statistical Package for the Social Sciences (SPSS) version 24 (IBM corporation, Armonk, NY). Each year's data was collated into a single dataset.

All patients were removed except for those with a primary diagnosis code for AMI from 1st January 2004 to 30th September 2015. Admissions from the final quarter of 2015 (1st October to 31st December) were excluded from the analysis because they were coded using ICD-10-CM/PCS. All elective admission and patients under the age of 18 years old were also excluded.

Sampling weights provided by the AHRQ were applied to the data to transform the 20% sample of AMI cases into a dataset that is nationally representative to the US. All subsequent analyses were of the weighted sample of AMI cases.

2.9.2 Aim 1: To describe prevalence of AMI and OA in the NIS between 2004 and 2015.

Basic statistics were used to describe the weighted sample of cases of AMI between 2004 and 2015. Differences between the OA and non-OA groups were examined with respect to baseline demographics, past medical history, and comorbidities. Categorical variables were reported as counts and proportions and compared using the Chi-squared test. Continuous variables were reported as means (with standard deviations) or medians (with interquartile ranges) and compared by the independent samples t-tests.

In order to investigate the prevalence of AMI over time, the total number of cases of AMI were reported for each year between 2004 and 2015. In order to investigate the prevalence of OA in people diagnosed with AMI, the proportion of AMI cases that had a concurrent diagnosis of OA was reported as a proportion with 95% confidence intervals for each year between 2004 and 2015. Linear regression, where the dependent variable was OA and the independent variable was the year of admission, determined whether there was an overall difference in OA

prevalence between 2004 and 2015. In order to account for sex and age differences in OA prevalence, these two covariates were included as independent variables in the linear regression model.

2.9.3 Aim 2: To determine the strength and direction of the association between a concurrent OA diagnosis and invasive management strategies following a diagnosis of AMI.

Using all cases of AMI in the NIS between 2004 and 2015, the association between OA and the following invasive management strategies were investigated:

- Coronary angiography (CA)
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass grafting (CABG)

Firstly, the number and proportion of patients that have received each invasive management strategy following AMI was calculated overall and stratified by sex and age. Sex was categorised to male and female. Age was categorised into 5 age bands: less than 50 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, and more than 80 years. The Chi-squared test determined whether there were sex differences in receiving invasive management strategies.

Next, differences in the proportion of patients receiving each invasive management strategy between the OA and non-OA groups was examined using the Chi-squared test. Both groups were also stratified by sex and age. The purpose of stratifying the cohort was to identify whether either of these variables confound or moderate the relationship between OA and each invasive management strategy.

Thirdly, the strength and direction of the association between OA and each invasive management strategy following a diagnosis of AMI was examined by unadjusted binary logistic regression. In each logistic regression model OA was the independent variable and each

invasive management strategy was the dependent variable. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI), where the OR represents the odds a person with OA had of receiving the invasive management strategy relative to a person without OA.

Fourthly, adjusted binary logistic regression determined whether OA was significantly associated with each invasive management strategy. Models were adjusted for demographics (age, sex, smoking status, income, payer, hospital bed size, hospital region, and year), past medical history (previous IHD, previous AMI, previous CABG, previous stroke or TIA, previous PCI), and comorbidities (AIDS, alcohol abuse, anaemia, heart failure, chronic lung disease, coagulopathies, diabetes mellitus, depression, substance misuse, hypertension, hypothyroid, liver disease, lymphoma, electrolyte disorders, metastatic cancer, neurological conditions, obesity, paralysis, peripheral vascular disease, psychoses, pulmonary circulation disorders, renal failure, solid tumour with no metastases, peptic ulcer disease, valvular heart disease, weight loss, and dementia). Previous studies of AMI in the NIS have included similar covariates in logistic regression models (Bharadwaj et al., 2019; Mohamed et al., 2019).

Fifthly, adjusted binary logistic regression determined whether OA was significantly associated with each invasive management strategy after stratification by sex and age. Sex was categorised into males and females. Age was categorised into the same 5 previously mentioned age bands.

Sixthly, adjusted binary logistic regression determined the association between OA and each invasive management strategy following AMI for each year between 2004 and 2015. This analysis determined whether the association between OA and the receipt of invasive management strategies had changed over time.

Finally, considering the entire NIS from 2004 to 2015, a sensitivity analysis of the OA variable was performed using the symptomatic OA variable. Both variables were compared with respect to demographics and the receipt of invasive management strategies.

2.9.4 Aim 3: To determine the strength and direction of the association between a concurrent OA diagnosis and adverse clinical outcomes following a diagnosis of AMI.

The relationships between OA and the following adverse clinical outcomes were investigated:

- In-hospital mortality
- Major acute cardiovascular and cerebrovascular events
- All-cause bleeding
- Stroke or TIA

Similar to aim 2, the number and proportion of patients experiencing each adverse outcome following AMI was calculated overall and stratified by sex and age. Sex was categorised into males and females and age was categorised into the same 5 previously mentioned age bands. The Chi-squared test determined whether there were sex differences in experiencing adverse clinical outcomes.

Secondly, a comparison of the proportion of patients experiencing each adverse clinical outcome between the OA and non-OA groups was made using the Chi-squared test. Both groups were also stratified by sex and age.

Thirdly, the strength and direction of the association between OA and each adverse clinical outcome following a diagnosis of AMI was examined by unadjusted binary logistic regression. In each logistic regression model OA was the independent variable and each adverse clinical outcome was the dependent variable. Results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI), where the OR represents the odds a person with OA had of experiencing the adverse clinical outcome relative to a person without OA.

Fourthly, adjusted binary logistic regression determined whether OA was significantly associated with each adverse clinical outcome. As in aim 2, models were adjusted for demographics, past medical history and comorbidities. Additionally, these models were

adjusted for the diagnosis codes for cardiac arrest and the procedural codes for the receipt of PCI, CABG, and intra-aortic balloon pump or ventricular assist device (IABP) (ICD-9-CM codes 37.68 and 37.61). These additional covariates were included because they were likely to be significantly associated with the four adverse clinical outcomes.

Fifthly, adjusted binary logistic regression determined whether OA was significantly associated with each adverse clinical outcome after stratification by sex and age. Sex was categorised into males and females. Age was categorised into the same 5 previously mentioned age bands.

Sixthly, adjusted binary logistic regression determined the association between OA and each adverse clinical outcome following AMI for each year starting from 2004 to 2015. This analysis determined whether the association between OA and the experiencing adverse clinical outcomes had changed over time.

Finally, two sensitivity analyses were performed. First, the original OA and symptomatic OA variables were compared with respect to the proportion of AMI patients who experienced each adverse clinical outcome.

A second sensitivity analysis was performed to determine the effect of the removal of patient identifiers within the NIS, as this means that multiple hospitalisations for AMI may have originated from the same patient, potentially biasing the results. This effect was investigated by performing adjusted binary logistic regression between OA and each adverse clinical outcome after excluding all cases with a previous history of AMI.

3 Chapter 3: Results

3.1 Aim 1: To describe prevalence of AMI and OA in the NIS between 2004 and 2015.

3.1.1 AMI cohort demographics

Between 2004 and 2015, there were 1,464,186 hospital discharges with the primary diagnosis code of AMI. Applying discharge weights provided by the AHRQ produced a weighted sample of 7,053,475 AMI hospital discharges. All subsequent estimates are based on this weighted sample. After the exclusion of elective admissions and people under 18 years old, there were 6,561,940 cases of AMI (Table 3.1). The mean age was 67.6 years (standard deviation (SD) 14.4 years), the median age was 68 years (interquartile range 57 to 79), and 39.8% of cases were female. Twenty-eight percent were current or ex-smokers. Most patients were White (76.8%), followed by Black (10.0%), and Hispanic (7.4%). In terms of cardiovascular disease history, 76.5% had a history of IHD, 8.7% had a previous AMI, 9.8% had a previous PCI, 6.1% had a previous CABG, and 3.1% had a previous stroke or TIA.

3.1.2 Osteoarthritis

Of the 6,561,940 patients who had an AMI between 2004 and 2015, 414,072 (6.31%; 95% CI 6.29%, 6.33%) had a concurrent diagnosis of OA (Table 3.1). Compared to the non-OA group, the OA group was older (mean age 75.3, SD 12.3 years-old; versus 67.1, SD 14.4 years-old), had more females (56.3% versus 38.7%), fewer smokers (22.7% versus 28.8%), more Whites (81.9% versus 76.4%), more payers through Medicare (77.4% versus 56.2%), and fewer payers through private insurance (15.6% versus 28.2%) ($p<0.001$ for all).

The OA group more frequently experienced a previous AMI (9.3% versus 8.6%) and stroke or TIA (4.0% versus 3.0%), however, they were less likely to have had a previous PCI (8.9% versus 9.8%), previous CABG (5.7% versus 6.2%), or previous history of IHD (74.9% versus 76.6%)

(p<0.001 for all) (Table 3.1). Additionally, the OA group had a higher prevalence of comorbidities, including heart failure (35.8% versus 31.3%), chronic lung disease (25.5% versus 20.4%), peripheral vascular disease (13.7% versus 10.8%), obesity (15.8% versus 11.8%), and hypertension (75% versus 66.5%) (p<0.001 for all).

Table 3.1: Baseline demographics of OA cases.

		Entire AMI cohort				No OA				OA			
		Count	Column N %	Mean	Standard Deviation	Count	Column N %	Mean	Standard Deviation	Count	Column N %	Mean	Standard Deviation
Count		6561940 (100%)				6147868 (93.7%)				414072 (6.3%)			
Age				68	14			67	14			75	12
Sex	Female	2610000	39.8%			2376838	38.7%			233162	56.3%		
Race	White	4221763	76.8%			3931018	76.4%			290745	81.9%		
	Black	548050	10.0%			518348	10.1%			29703	8.4%		
	Hispanic	407959	7.4%			388022	7.5%			19938	5.6%		
	Asian or Pacific Islander	124334	2.3%			118518	2.3%			5816	1.6%		
	Native American	29200	0.5%			27693	0.5%			1507	0.4%		
	Other	168361	3.1%			161152	3.1%			7209	2.0%		
History of Smoking		1865067	28.4%			1770980	28.8%			94087	22.7%		
Payer for healthcare	Medicare	3773955	57.5%			3453446	56.2%			320508	77.4%		
	Medicaid	402138	6.1%			388020	6.3%			14118	3.4%		
	Private Insurance	1798636	27.4%			1734054	28.2%			64582	15.6%		
	Self-pay	374848	5.7%			367581	6.0%			7267	1.8%		
	No charge	36935	0.6%			36187	0.6%			748	0.2%		
	Other	175428	2.7%			168580	2.7%			6849	1.7%		
	Missing	1167248	17.8%			1106676	18.0%			60573	14.6%		

ZIP code income quartile	0-25th percentile (lowest income)	1545991	23.6%			1439913	23.4%			106077	25.6%		
	26th-50th percentile	1463494	22.3%			1364268	22.2%			99225	24.0%		
	51st-75th percentile	1292086	19.7%			1208882	19.7%			83204	20.1%		
	76th-100th percentile (highest income)	1093122	16.7%			1028130	16.7%			64992	15.7%		
Hospital bed size	Small	696162	10.7%			648408	10.6%			47754	11.6%		
	Medium	1608785	24.6%			1502044	24.5%			106741	25.9%		
	Large	4231664	64.7%			3973614	64.9%			258050	62.6%		
Hospital region	Northeast	1289577	19.7%			1221628	19.9%			67949	16.4%		
	Midwest	1524853	23.2%			1408491	22.9%			116362	28.1%		
	South	2593053	39.5%			2434820	39.6%			158233	38.2%		
	West	1154457	17.6%			1082930	17.6%			71527	17.3%		
Previous MI		568827	8.7%			530503	8.6%			38324	9.3%		
History of IHD		5017145	76.5%			4707132	76.6%			310013	74.9%		
Previous PCI		639853	9.8%			603193	9.8%			36661	8.9%		
Previous CABG		403488	6.1%			379718	6.2%			23770	5.7%		
Previous stroke		203267	3.1%			186821	3.0%			16446	4.0%		
Year	2004	596292	9.1%			565290	9.2%			31002	7.5%		
	2005	570956	8.7%			541386	8.8%			29570	7.1%		
	2006	581741	8.9%			551640	9.0%			30101	7.3%		
	2007	534651	8.1%			503507	8.2%			31145	7.5%		
	2008	562480	8.6%			529657	8.6%			32823	7.9%		
	2009	553088	8.4%			516306	8.4%			36782	8.9%		
	2010	523463	8.0%			487912	7.9%			35551	8.6%		

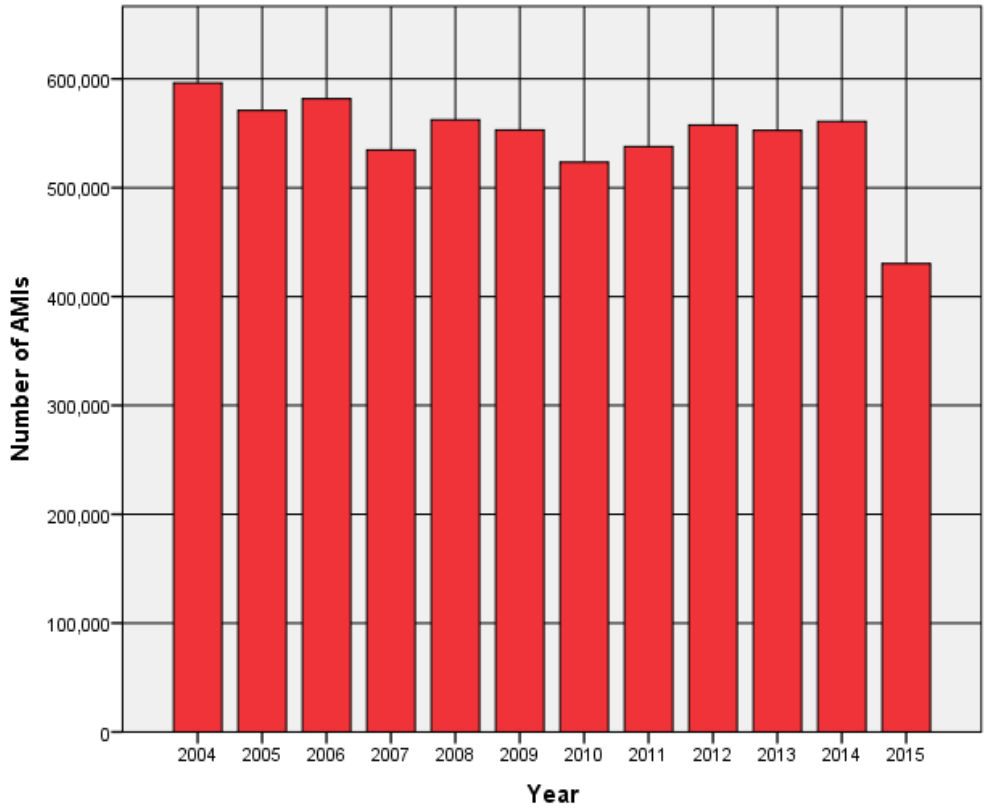
	2011	537733	8.2%			498966	8.1%			38766	9.4%		
	2012	557605	8.5%			518120	8.4%			39485	9.5%		
	2013	552710	8.4%			513510	8.4%			39200	9.5%		
	2014	560890	8.5%			521545	8.5%			39345	9.5%		
	2015	430330	6.6%			400030	6.5%			30300	7.3%		
Comorbidities	AIDS	8391	0.1%			8212	0.1%			179	0.0%		
	Alcoholism	187298	2.9%			180147	2.9%			7150	1.7%		
	Anaemia	1036487	15.8%			946156	15.4%			90331	21.8%		
	Rheumatic conditions	144455	2.2%			128299	2.1%			16156	3.9%		
	Heart failure	2069624	31.5%			1921263	31.3%			148360	35.8%		
	Chronic lung disease	1358739	20.7%			1253218	20.4%			105520	25.5%		
	Coagulopathies	288569	4.4%			271458	4.4%			17110	4.1%		
	Diabetes	2255254	34.4%			2112727	34.4%			142526	34.4%		
	Depression	428891	6.5%			379322	6.2%			49569	12.0%		
	Drug misuse	137020	2.1%			132559	2.2%			4460	1.1%		
	Hypertension	4398845	67.0%			4088085	66.5%			310761	75.0%		
	Hypothyroidism	647286	9.9%			579774	9.4%			67512	16.3%		
	Liver disease	79833	1.2%			75258	1.2%			4575	1.1%		
	Lymphoma	32739	0.5%			30558	0.5%			2181	0.5%		
	Fluid and electrolyte disorders	1293118	19.7%			1203785	19.6%			89333	21.6%		
	Metastatic cancer	58016	0.9%			54902	0.9%			3114	0.8%		
	Neurological conditions	386469	5.9%			352932	5.7%			33537	8.1%		
	Obesity	788554	12.0%			723244	11.8%			65310	15.8%		
	Paralysis	107130	1.6%			100014	1.6%			7116	1.7%		

	Peripheral vascular disease	718119	10.9%			661370	10.8%			56749	13.7%		
	Psychosis	137507	2.1%			126371	2.1%			11135	2.7%		
	Pulmonary circulation disorders	6531	0.1%			6152	0.1%			379	0.1%		
	Renal failure	1111786	16.9%			1028977	16.7%			82810	20.0%		
	Solid tumour, no metastases	94067	1.4%			87836	1.4%			6232	1.5%		
	Peptic ulcer disease	2206	0.0%			1940	0.0%			266	0.1%		
	Valvular heart disease	15685	0.2%			14833	0.2%			852	0.2%		
	Weight loss	144597	2.2%			134504	2.2%			10092	2.4%		
	Dementia	116788	1.8%			104255	1.7%			12533	3.0%		

3.1.3 Temporal Trends

The total number of AMI's per year remained similar over time with 596,292 cases in 2004 and 560,890 in 2014 (Figure 3.1). As previously mentioned, in October 2015 the NIS switched from ICD-9-CM to ICD-10-CM/PCS codes. This study only searched for ICD-9-CM codes, therefore admissions from the final quarter of 2015 were not captured, resulting in an approximately 25% decline in the number of AMI cases in 2015.

Figure 3.1: Crude number of AMI cases per year.



The crude number of OA cases among the AMI cohort increased from 31,002 cases in 2004 to 39,345 cases in 2014 (Figure 3.2). There was a decrease in the crude number of OA cases between 2014 and 2015 due to the change to ICD-10-CM/PCS. The prevalence of OA among AMI patients rose significantly from 5.20% (95% CI 5.14 to 5.26) in 2004 to 7.04% (6.96 to 7.12) in 2015 (Figure 3.3). Most of this increase occurred between 2006 and 2011 where the prevalence of OA increased significantly from 2006 to 2007 (5.17% (5.12 to 5.23) to 5.82% (5.76 to 5.89)) and in each consecutive year from 2008 to 2011 (5.84% (5.77 to 5.90), 6.65%

(6.58 to 6.71), 6.79% (6.72 to 6.86), and 7.21% (7.14, 7.28), respectively). The prevalence remained relatively stable between 2004 and 2006 and 2011 and 2015. When considering the entire study period, linear regression identified a significant difference in the prevalence of OA cases among AMI patients ($p<0.001$) in both unadjusted and adjusted models.

Compared to OA cases in 2004 to 2006, cases in 2011 to 2015 had fewer females, fewer Whites, more people paying with Medicare or Medicaid, fewer people paying out of pocket or with private insurance, more smokers, a lower average income based on ZIP code, and were younger (Table 3.2).

Table 3.2: Comparing the OA cohort between 2004 to 2006 and 2011 to 2015.

		OA cases 2004-2006	**OA cases 2011-2015**
Count		90,674	187,097
Age		75.6 (SD 12.4)	74.9 (SD 12.0)
Sex	**Male**	41.3%	45.8%
	Female	58.7%	54.2%
Race	**White**	84.4%	80.6%
	Black	6.5%	9.3%
	Hispanic	5.6%	5.9%
	Asian or Pacific Islander	1.3%	1.7%
	Native American	0.2%	0.4%
	Other	2.0%	2.0%
Payer	**Medicare**	77.5%	77.9%
	Medicaid	2.9%	4.0%
	Private Insurance	16.2%	14.6%

	Self-pay	1.6%	1.7%
	No charge	0.2%	0.2%
	Other	1.5%	1.7%
Smoking history		19.6%	24.8%
Days in hospital		4.6 (SD 3.8)	4.6 (SD 4.3)
Income quartile by ZIP code	**0-25th**	27.1%	31.2%
	26th-50th	28.0%	27.4%
	51st-75th	24.4%	23.7%
	76th-100th	20.5%	17.7%

Figure 3.2: Crude number of OA cases per year.

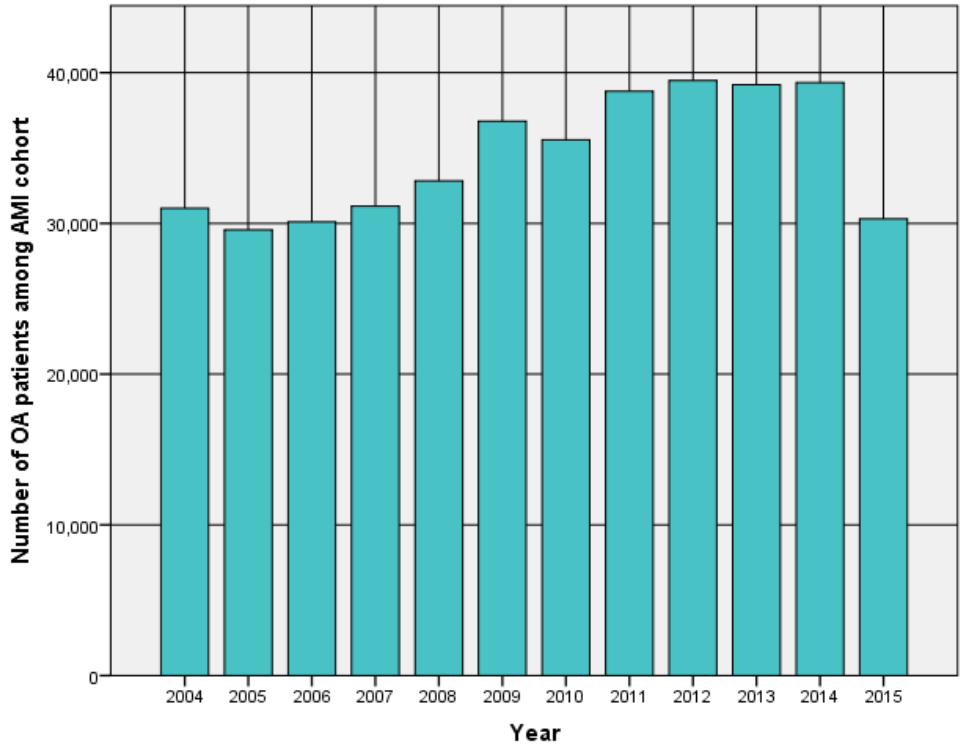
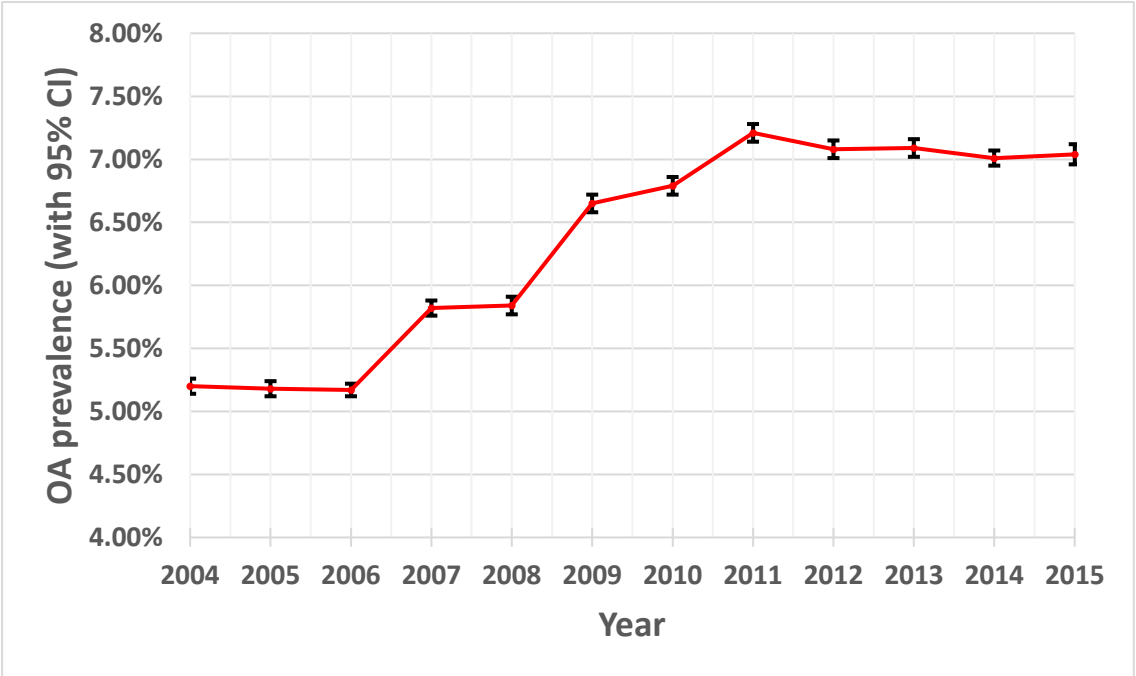


Figure 3.3: The prevalence of OA in AMI by year with 95% confidence intervals.



3.2 Aim 2: To determine the strength and direction of the association between a concurrent OA diagnosis and invasive management strategies following a diagnosis of AMI.

3.2.1 Proportion receiving invasive management strategies

Of all cases of AMI, 64.6% received CA, 42.9% received PCI, and 8.4% received CABG (Table 3.3). Stratification by sex showed that men were more likely to receive CA (69.8% versus 56.6%), PCI (48.6% versus 34.2%), and CABG (10.0% versus 6.0%). Stratification by age showed that advanced age was associated with a decreased likelihood of receiving CA and PCI. The oldest age band (80 years and older) had the lowest likelihood of receiving CA and PCI (36.6% and 21.7% respectively). Each subsequently younger age band was more likely to receive CA and PCI, with the highest prevalence of both management strategies seen in people under 50 years old (81.5% had CA and 60.2% had PCI). Age also affected the likelihood of receiving CABG, where the 60 to 69-year-old age band was most likely to receive CABG (11.4%) and the oldest (3.7%) and youngest (6.9%) age bands were least likely to receive CABG.

3.2.2 Proportion receiving invasive management strategies by OA status

Compared to non-OA cases, OA cases were less likely to receive invasive management strategies including CA (55.1% versus 65.2%), PCI (33.1% versus 43.5%), and CABG (7.4% versus 8.5%) following AMI (Table 3.3 and Figure 3.4). Both men and women with OA were less likely than their non-OA counterparts to receive CA (63.3% versus 70.1% and 48.8% versus 57.4%, respectively) and PCI (40.0% versus 49.0% and 27.8% versus 34.9%, respectively). However, women with OA were less likely to receive CABG (5.0% versus 6.1%) than women without OA and men with OA were more likely to receive CABG (10.5% versus 10.0%) than men without OA. Stratification by age showed that people with OA were less likely to receive invasive management strategies except for the following differences. For people aged less than 50 and 50 to 59 years old, people with OA were more likely to receive CABG (8.6% versus 6.8% and

11.9% versus 9.9%, respectively) than people without OA. People aged 60 to 69 with OA had a similar likelihood of having CA (74.2% versus 74.0%) and CABG (12.0% versus 11.4%) compared to people without OA. People aged 70 to 79 with OA also had a similar likelihood of receiving CA (64.6% versus 63.7%) compared to people without OA.

Table 3.3: The receipt of invasive management strategies between OA and non-OA cases overall and stratified by sex and age.

Entire cohort:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	4236305	64.6%	4008011	65.2%	228295	55.1%
PCI	2812655	42.9%	2675574	43.5%	137081	33.1%
CABG	553254	8.4%	522641	8.5%	30613	7.4%
Men:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	2758377	69.8%	2643885	70.1%	114493	63.3%
PCI	1919056	48.6%	1846763	49.0%	72293	40.0%
CABG	396409	10.0%	377485	10.0%	18924	10.5%
Women:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	1477928	56.6%	1364126	57.4%	113802	48.8%
PCI	893598	34.2%	828811	34.9%	64788	27.8%
CABG	156845	6.0%	145156	6.1%	11689	5.0%
Under 50 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	612216	81.5%	603683	81.5%	8533	80.0%
PCI	452006	60.2%	446252	60.3%	5754	53.9%
CABG	51562	6.9%	50649	6.8%	913	8.6%
50 to 59 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	1019776	79.8%	987734	79.8%	32042	79.1%
PCI	736619	57.6%	715429	57.8%	21190	52.3%
CABG	127421	10.0%	122591	9.9%	4831	11.9%

60 to 69 years old:

	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	1103900	74.0%	1047005	74.0%	56895	74.2%
PCI	730700	49.0%	695426	49.1%	35274	46.0%
CABG	170514	11.4%	161302	11.4%	9212	12.0%

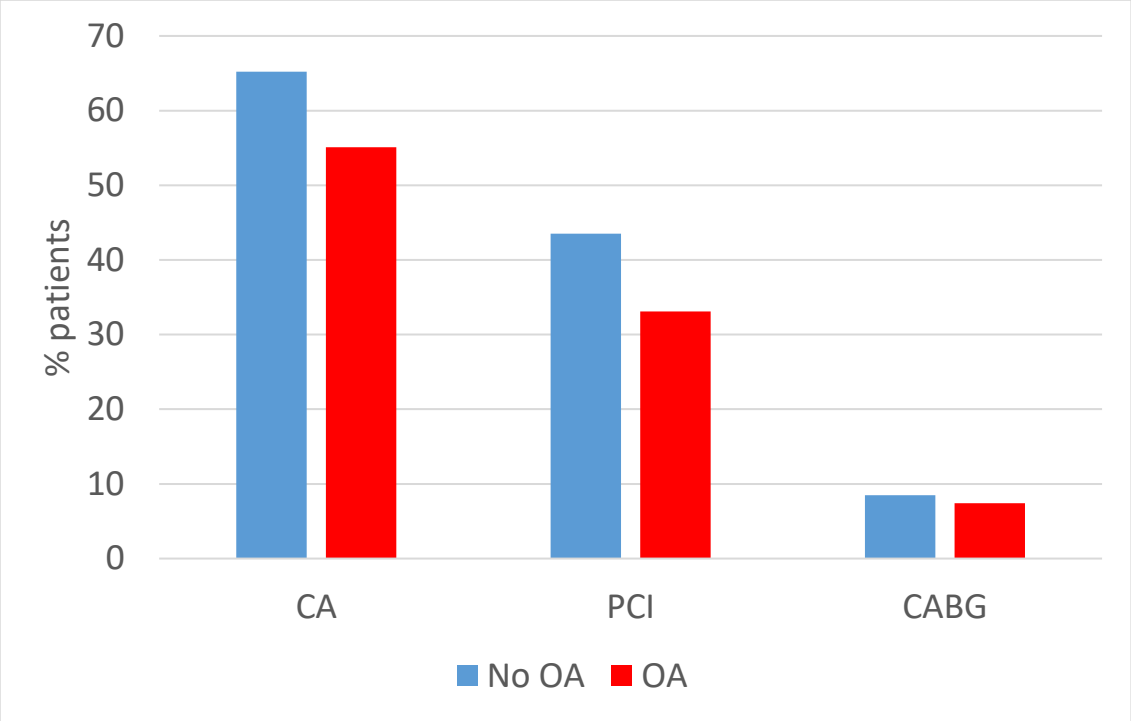
70 to 79 years old:

	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	910088	63.8%	840715	63.7%	69373	64.6%
PCI	542635	38.0%	503400	38.1%	39235	36.5%
CABG	144639	10.1%	134180	10.2%	10459	9.7%

Over 80 years old:

	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
CA	590325	36.6%	528872	36.9%	61452	34.4%
PCI	350695	21.7%	315067	22.0%	35628	19.9%
CABG	59118	3.7%	53920	3.8%	5198	2.9%

Figure 3.4: The receipt of invasive management strategies between OA and non-OA cases.



3.2.3 Association between OA and invasive management strategies

Unadjusted binary logistic regression showed that people with OA were associated with a decreased odds of receiving CA (odds ratio 0.656; 95% confidence interval 0.652, 0.660), PCI (0.642; 0.638, 0.647) and CABG (0.859; 0.849, 0.870). After adjustment for confounders, OA remained significantly associated with a decreased odds of receiving CA (0.909; 0.903, 0.916), PCI (0.873; 0.866, 0.879), and CABG (0.983; 0.971, 0.996). The extent of co-occurrence between the OA variable and the other rheumatological conditions (which was not included in the binary logistic regression models) is presented in Table 3.4. This table shows that of all people with an ICD-9-CM diagnosis code for OA (n=414,071), only 3.9% (n=16,156) were considered to have another rheumatological condition. This suggests there to be minimal co-occurrence between the two variables. This also suggests that one or both variables may not be completely valid because one would expect there to be at least as many individuals with a rheumatological condition as there were an OA diagnosis because rheumatological conditions encompass OA as well as many other conditions (including RA, PsA, etc).

Table 3.4: The co-occurrence between the OA and other rheumatological conditions.

		ICD-9-CM coded OA variable		
		Yes	No	
Rheumatological conditions	Yes	16,156 (0.25%)	128,299 (1.96%)	144,455 (2.20%)
	No	397,915 (6.06%)	6,019,570 (91.73%)	6,417,485 (97.80%)
		414,071 (6.31%)	6,147,869 (93.69%)	6,561,940

3.2.4 Association between OA and invasive management strategies – stratified by sex

After stratifying by sex, adjusted binary logistic regression showed both men and women with OA to be associated with a decreased odds of CA (0.929; 0.918, 0.940; and 0.910; 0.901, 0.919) and PCI (0.877; 0.868, 0.887; and 0.866; 0.857, 0.876) relative to men and women without OA, respectively (Table 3.5). However, the association with CABG differed by sex, as men with OA were associated with an increased odds of CABG (1.039; 1.022, 1.056) compared to men without OA and women with OA had a decreased odds of CABG (0.941; 0.922, 0.960) compared to women without OA.

3.2.5 Association between OA and invasive management strategies – stratified by age

Similar to the unstratified results, people with OA were associated with a decreased odds of CA and PCI compared to people without OA in every age band (Table 3.5). The age band that was most strongly associated with a decreased odds of CA was the oldest age band (0.913; 0.902, 0.924) and the age band that was most strongly associated with a decreased odds of PCI was the youngest age band (0.801; 0.768, 0.836). The effect of OA on receiving CABG changed with age. OA was significantly associated with an increased odds of CABG In the youngest three age bands and significantly associated with a decreased odds of CABG in the oldest age band.

Table 3.5: The association between OA and invasive management strategies overall and stratified by sex and age.

Independent variable:		Dependent variables:					
Osteoarthritis		**Coronary angiography**		**Percutaneous coronary intervention**		**Coronary artery bypass grafting**	
		Unadjusted OR	**Adjusted OR**	**Unadjusted OR**	**Adjusted OR**	**Unadjusted OR**	**Adjusted OR**
Overall		0.656 (0.652, 0.660)	0.909 (0.903, 0.916)	0.642 (0.638, 0.647)	0.873 (0.866, 0.879)	0.859 (0.849, 0.870)	0.983 (0.971, 0.996)
Sex							
	Male	0.735 (0.728, 0.742)	0.929 (0.918, 0.940)	0.694 (0.687, 0.700)	0.877 (0.868, 0.887)	1.050 (1.034, 1.067)	1.039 (1.022, 1.056)
	Female	0.708 (0.702, 0.714)	0.910 (0.901, 0.919)	0.719 (0.712, 0.726)	0.866 (0.857, 0.876)	0.811 (0.796, 0.827)	0.941 (0.922, 0.960)
Age							
	Younger than 50 years old	0.904 (0.862, 0.948)	0.922 (0.874, 0.972)	0.771 (0.742, 0.802)	0.801 (0.768, 0.836)	1.275 (1.191, 1.365)	1.075 (1.000, 1.155)
	50 to 59 years old	0.955 (0.933, 0.979)	0.950 (0.925, 0.976)	0.800 (0.784, 0.816)	0.851 (0.832, 0.869)	1.231 (1.194, 1.269)	1.195 (1.157, 1.234)
	60 to 69 years old	1.013 (0.996, 1.030)	0.964 (0.946, 0.982)	0.882 (0.870, 0.895)	0.889 (0.875, 0.903)	1.062 (1.038, 1.086)	1.066 (1.041, 1.091)
	70 to 79 years old	1.042 (1.028, 1.056)	0.958 (0.944, 0.972)	0.935 (0.923, 0.947)	0.883 (0.871, 0.896)	0.954 (0.934, 0.974)	1.001 (0.980, 1.024)

	Older than 80 years old	0.896 (0.886, 0.905)	0.913 (0.902, 0.924)	0.883 (0.873, 0.894)	0.882 (0.870, 0.894)	0.766 (0.744, 0.788)	0.906 (0.878, 0.934)

3.2.6 Annual association between OA and invasive management strategies – 2004 to 2015

The overall association between OA and CA and PCI following AMI remained relatively constant from 2004 to 2015 (Table 3.6). However, the odds of receiving CABG appeared to increase over time from 2004 to 2015, changing from a decreased odds before 2009 to an increased odds after 2010.

Table 3.6: The adjusted odds of receiving invasive management strategies among OA cases relative to non-OA cases stratified by year.

Adjusted odds of invasive management strategies for people with OA stratified by year				
Year	**Number of AMI cases**	**CA**	**PCI**	**CABG**
2004-2015	6561940	0.909 (0.903, 0.916)	0.873 (0.866, 0.879)	0.983 (0.971, 0.996)
2004	596292	0.893 (0.869, 0.918)	0.868 (0.843, 0.893)	0.926 (0.885, 0.969)
2005	570956	0.847 (0.823, 0.871)	0.832 (0.808, 0.856)	0.846 (0.806, 0.889)
2006	580129	0.842 (0.819, 0.866)	0.822 (0.799, 0.846)	0.923 (0.881, 0.967)
2007	533970	0.926 (0.900, 0.952)	0.829 (0.806, 0.853)	0.944 (0.901, 0.990)
2008	561863	0.922 (0.898, 0.948)	0.891 (0.867, 0.916)	0.889 (0.849, 0.932)
2009	543755	0.964 (0.939, 0.989)	0.899 (0.867, 0.912)	1.103 (1.059, 1.148)
2010	517049	0.895 (0.872, 0.919)	0.870 (0.848, 0.893)	0.921 (0.880, 0.964)
2011	531064	0.942 (0.919, 0.966)	0.941 (0.918, 0.965)	1.013 (0.970, 1.058)
2012	557605	0.913 (0.890, 0.936)	0.854 (0.834, 0.875)	1.090 (1.046, 1.136)
2013	552710	0.940 (0.917, 0.964)	0.883 (0.862, 0.904)	1.031 (0.990, 1.075)
2014	560890	0.930 (0.907, 0.953)	0.878 (0.858, 0.899)	1.021 (0.980, 1.064)
2015	430330	0.944 (0.918, 0.972)	0.863 (0.841, 0.887)	1.143 (1.092, 1.195)

3.2.7 Sensitivity analysis of the OA variable using symptomatic OA

A comparison of both definitions of OA showed them to be similar in most regards. The proportion of AMI patients with symptomatic OA was 6.77% (95% CI 6.75%, 6.79%) (n=444,217) compared to 6.31% using the original definition of OA (Table 3.7). The mean age of the symptomatic OA group was 75.1 years (SD 12.3) which was similar to the original OA group (75.3 years, SD 12.3). The symptomatic OA group had slightly fewer females (55.7% versus 56.3%) and slightly more smokers (22.9% versus 22.7%) than the original OA definition.

There was a similar proportion of people in the symptomatic OA group and the original OA group who experienced a previous AMI (9.267% versus 9.255%), previous IHD (74.86% versus

74.87%), previous PCI (8.8% versus 8.9%), previous CABG (5.8% versus 5.7%), and previous stroke or TIA (3.95% versus 3.97%) (Table 3.7). The symptomatic OA and original OA groups also had similar proportions of comorbidities including heart failure (35.6% versus 35.8%), chronic lung disease (25.3% versus 25.5%), peripheral vascular disease (13.6% versus 13.7%), obesity (15.7% versus 15.8%), and hypertension (74.9% versus 75.0%).

The symptomatic and original OA groups received a similar proportion of invasive management strategies including CA (55.3% versus 55.1%), PCI (33.3% versus 33.1%), and CABG (7.35% versus 7.39%) (Table 3.7).

Table 3.7: The baseline demographics of the OA and symptomatic OA variables.

		OA				Symptomatic OA			
		Count	Column N %	Mean	Standard Deviation	Count	Column N %	Mean	Standard Deviation
Count and % of AMI cohort		414072	6.3%			444217	6.8%		
Age				75.3	12.3			75.1	12.3
Sex	Male	180909	43.7%			196770	44.3%		
	Female	233162	56.3%			247447	55.7%		
Race	White	290745	81.9%			310927	81.6%		
	Black	29703	8.4%			32441	8.5%		
	Hispanic	19938	5.6%			21668	5.7%		
	Asian or Pacific Islander	5816	1.6%			6377	1.7%		
	Native American	1507	0.4%			1627	0.4%		
	Other	7209	2.0%			7966	2.1%		
Smoking history		94087	22.7%			101734	22.9%		
Payer	Medicare	320508	77.4%			340756	76.7%		
	Medicaid	14118	3.4%			15848	3.6%		
	Private insurance	64582	15.6%			70771	15.9%		
	Self-pay	7267	1.8%			8444	1.9%		
	No charge	748	0.2%			824	0.2%		
	Other	6849	1.7%			7574	1.7%		
Income quartile (by ZIP code)	Unknown	60573	14.6%			63345	14.3%		
	0-25th percentile (lowest income)	106077	25.6%			113970	25.7%		

	26th to 50th percentile	99225	24.0%			107158	24.1%		
	51st to 75th percentile	83204	20.1%			89763	20.2%		
	76th to 100th percentile (highest income)	64992	15.7%			69982	15.8%		
Hospital bedsize	Small	47754	11.6%			51309	11.6%		
	Medium	106741	25.9%			114261	25.8%		
	Large	258050	62.6%			277007	62.6%		
Hospital region	Northeast	67949	16.4%			72273	16.3%		
	Midwest	116362	28.1%			124564	28.0%		
	South	158233	38.2%			169710	38.2%		
	West	71527	17.3%			77671	17.5%		
Previous AMI		38324	9.3%			41168	9.3%		
History of IHD		310013	74.9%			332581	74.9%		
Previous PCI		36661	8.9%			39241	8.8%		
Previous CABG		23770	5.7%			25551	5.8%		
Previous stroke/TIA		16446	4.0%			17566	4.0%		
Year	2004	31002	7.5%			32461	7.3%		
	2005	29570	7.1%			30884	7.0%		
	2006	30101	7.3%			31738	7.1%		
	2007	31145	7.5%			32831	7.4%		
	2008	32823	7.9%			34981	7.9%		
	2009	36782	8.9%			39222	8.8%		
	2010	35551	8.6%			37947	8.5%		

	2011	38766	9.4%			41884	9.4%		
	2012	39485	9.5%			42745	9.6%		
	2013	39200	9.5%			42790	9.6%		
	2014	39345	9.5%			43395	9.8%		
	2015	30300	7.3%			33340	7.5%		
AIDS		179	0.0%			203	0.0%		
Alcoholism		7150	1.7%			8197	1.8%		
Anemia		90331	21.8%			97164	21.9%		
Rheumatological conditions		16156	3.9%			16987	3.8%		
Heart failure		148360	35.8%			158091	35.6%		
Chronic lung disease		105520	25.5%			112328	25.3%		
Coagulopathies		17110	4.1%			18652	4.2%		
Diabetes mellitus		142526	34.4%			153594	34.6%		
Depression		49569	12.0%			52576	11.8%		
Drug misuse		4460	1.1%			5111	1.2%		
Hypertension		310761	75.0%			332927	74.9%		
Hypothyroidism		67512	16.3%			71344	16.1%		
Liver disease		4575	1.1%			5059	1.1%		
Lymphoma		2181	0.5%			2387	0.5%		
Electrolyte or fluid disorders		89333	21.6%			96937	21.8%		
Metastatic cancer		3114	0.8%			3410	0.8%		
Neurological conditions		33537	8.1%			35934	8.1%		

Obesity		65310	15.8%			69553	15.7%		
Paralysis		7116	1.7%			7764	1.7%		
Peripheral vascular disease		56749	13.7%			60553	13.6%		
Psychosis		11135	2.7%			12075	2.7%		
Pulmonary circulation disorders		379	0.1%			422	0.1%		
Renal failure		82810	20.0%			89052	20.0%		
Solid tumour without metastases		6232	1.5%			6671	1.5%		
Peptic ulcer disease		266	0.1%			271	0.1%		
Valvular heart disease		852	0.2%			946	0.2%		
Weight loss		10092	2.4%			11076	2.5%		
Dementia		12533	3.0%			13386	3.0%		
CA		228295	55.1%			245815	55.3%		
PCI		137081	33.1%			147930	33.3%		
CABG		30613	7.4%			32656	7.4%		
In-hospital mortality		19763	4.8%			20856	4.7%		
MACCE		25369	6.1%			27004	6.1%		
All-cause bleeding		10224	2.5%			11072	2.5%		
Stroke or TIA		6227	1.5%			6774	1.5%		

3.3 Aim 3: To determine the strength and direction of the association between a concurrent OA diagnosis and adverse clinical outcomes following a diagnosis of AMI.

3.3.1 Proportion of cases experiencing adverse clinical outcomes

Of all cases of AMI, 5.8% died in-hospital, 7.1% suffered from MACCE, 3.2% suffered from bleeding, and 1.5% suffered from stroke or TIA (Table 3.8). Stratification by sex showed that women were more likely to suffer from mortality (6.9% versus 5.1%), MACCE (8.6% versus 6.1%), all-cause bleeding (3.4% versus 3.0%), and stroke or TIA (2.0% versus 1.2%). Stratification by age showed that advanced age was associated with an increased likelihood of experiencing each adverse clinical outcome. The oldest age band had the highest proportion of in-hospital mortality (11.1%), MACCE (13.0%), all-cause bleeding (4.2%), and stroke or TIA (2.3%) and the lowest age band had the lowest proportion of each adverse clinical outcome (1.7%, 2.3%, 1.7%, and 0.6%, respectively).

3.3.2 The proportion of cases receiving adverse clinical outcomes by OA status

Compared to non-OA cases, the proportion of patients with OA who suffered a stroke or TIA was similar (1.50% versus 1.51%) and a lower proportion of OA cases experienced in-hospital mortality (4.8% versus 5.9%), MACCE (6.1% versus 7.2%), and all-cause bleeding (2.5% versus 3.2%) following AMI (Table 3.8 and Figure 3.5). Similar to the unstratified sample, both men and women with OA were less likely to experience in-hospital mortality (4.0% versus 5.1% and 5.4% versus 7.0%, respectively), MACCE (5.0% versus 6.2% and 7.0% versus 8.7%, respectively), and all-cause bleeding (2.3% versus 3.1% and 2.6% versus 3.4%, respectively) than their non-OA counterparts. Both men and women with OA had a similar likelihood of experiencing stroke or TIA compared to their non-OA counterparts (1.1% versus 1.2% and 1.8% versus 2.0%, respectively). Stratification by age showed that people with OA were less likely to suffer from

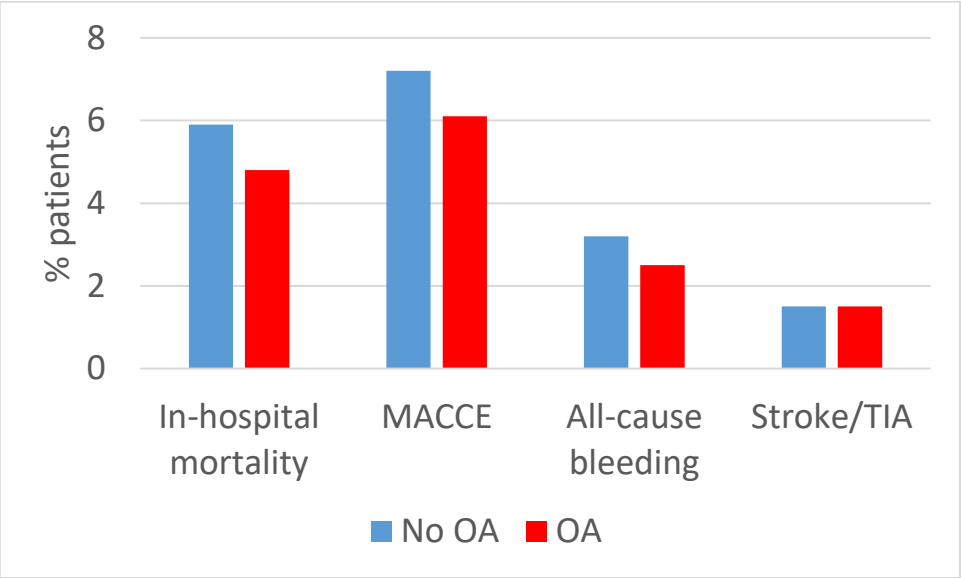
in-hospital mortality, MACCE, all-cause bleeding, and stroke or TIA than people without OA in every age band.

Table 3.8: The proportion of cases experiencing adverse clinical outcomes between OA and non-OA cases overall and stratified by sex and age.

Entire cohort:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	381400	5.8%	361638	5.9%	19763	4.8%
MACCE	466766	7.1%	441368	7.2%	25398	6.1%
All-cause bleeding	207713	3.2%	197489	3.2%	10224	2.5%
Stroke/TIA	99038	1.5%	92811	1.51%	6227	1.50%
Men:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	201419	5.1%	194130	5.1%	7288	4.0%
MACCE	242497	6.1%	233402	6.2%	9095	5.0%
All-cause bleeding	120050	3.0%	115843	3.1%	4207	2.3%
Stroke/TIA	47047	1.2%	45058	1.2%	1989	1.1%
Women:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	179982	6.9%	167507	7.0%	12475	5.4%
MACCE	224269	8.6%	207966	8.7%	16303	7.0%
All-cause bleeding	87663	3.4%	81646	3.4%	6017	2.6%
Stroke/TIA	51990	2.0%	47753	2.0%	4237	1.8%
Under 50 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	13102	1.7%	13013	1.8%	89	0.8%
MACCE	17029	2.3%	16902	2.3%	128	1.2%
All-cause bleeding	12711	1.7%	12584	1.7%	127	1.2%
Stroke/TIA	4277	0.6%	4238	0.6%	39	0.4%
50 to 59 years old:						
	All AMI		No OA		OA	

	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	33124	2.6%	32627	2.6%	497	1.2%
MACCE	43187	3.4%	42474	3.4%	712	1.8%
All-cause bleeding	26056	2.0%	25431	2.1%	625	1.5%
Stroke/TIA	11146	0.9%	10921	0.9%	225	0.6%
60 to 69 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	61542	4.1%	59968	4.2%	1573	2.1%
MACCE	79499	5.3%	77210	5.5%	2289	3.0%
All-cause bleeding	43507	2.9%	42107	3.0%	1399	1.8%
Stroke/TIA	19985	1.3%	19211	1.4%	775	1.0%
70 to 79 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	95050	6.7%	91314	6.9%	3736	3.5%
MACCE	118209	8.3%	113016	8.6%	5194	4.8%
All-cause bleeding	58054	4.1%	55152	4.2%	2902	2.7%
Stroke/TIA	26901	1.9%	25352	1.9%	1548	1.4%
Over 80 years old:						
	All AMI		No OA		OA	
	Count	Column N%	Count	Column N %	Count	Column N %
In-hospital mortality	178582	11.1%	164715	11.5%	13867	7.8%
MACCE	208841	13.0%	191766	13.4%	17075	9.5%
All-cause bleeding	67385	4.2%	62215	4.3%	5171	2.9%
Stroke/TIA	36729	2.3%	33089	2.3%	3639	2.0%

Figure 3.5: The proportion of OA and non-OA cases who suffered from adverse clinical outcomes



3.3.3 Association between OA and adverse clinical outcomes

In unadjusted models, there was no association between OA and stroke or TIA (0.996; 0.971, 1.022), however, OA was significantly associated with decreased odds of mortality (0.802; 0.790, 0.814), MACCE (0.845; 0.834, 0.856), and all-cause bleeding (0.763; 0.748, 0.778) (Table 3.9). After adjustment for confounders, the association between OA and better outcomes increased (in-hospital mortality: 0.680; 0.670, 0.691; MACCE: 0.709; 0.699, 0.719; all-cause bleeding: 0.757; 0.741, 0.772; stroke/TIA: 0.844; 0.822, 0.868).

3.3.4 Association between OA and adverse clinical outcomes – stratified by sex

Similar to the unstratified sample, stratification by sex showed that both men and women with OA were associated with a decreased odds of experiencing adverse clinical outcomes compared to people without OA (Table 3.9). In adjusted analysis, men with OA were less likely to suffer from adverse clinical outcomes compared to their non-OA counterparts than women were. Negative confounding was seen in both sexes for every outcome except for all-cause bleeding where it was observed in males only.

3.3.5 Association between OA and adverse clinical outcomes – stratified by age

In adjusted analysis, OA was associated with a decreased odds of adverse clinical outcomes in each age band (Table 3.9). However, there appeared to be a trend where OA was most strongly associated with a decreased odds of experiencing adverse clinical outcomes in the younger age bands and OA was least strongly associated with experiencing adverse clinical outcomes in the oldest age bands.

Table 3.9: The association between OA and adverse clinical outcomes overall and stratified by sex and age.

Independent variable:		**Dependent variables:**							
Osteoarthritis		**In-hospital mortality**		**MACCE**		**All-cause bleeding**		**Stroke or TIA**	
		Unadjusted OR	**Adjusted OR**	**Unadjusted OR**	**Adjusted OR**	**Unadjusted OR**	**Adjusted OR**	**Unadjusted OR**	**Adjusted OR**
Overall		0.802 (0.790, 0.814)	0.680 (0.670, 0.691)	0.845 (0.834, 0.856)	0.709 (0.699, 0.719)	0.763 (0.748, 0.778)	0.757 (0.741, 0.772)	0.996 (0.971, 1.022)	0.844 (0.822, 0.868)
Sex									
	Male	0.773 (0.755, 0.792)	0.679 (0.662, 0.697)	0.802 (0.785, 0.820)	0.700 (0.684, 0.716)	0.751 (0.728, 0.775)	0.712 (0.689, 0.735)	0.919 (0.879, 0.962)	0.826 (0.788, 0.865)
	Female	0.746 (0.732, 0.760)	0.687 (0.674, 0.701)	0.784 (0.771, 0.797)	0.720 (0.707, 0.733)	0.745 (0.725, 0.765)	0.816 (0.795, 0.839)	0.903 (0.875, 0.932)	0.854 (0.827, 0.883)
Age									
	Younger than 50 years old	0.471 (0.382, 0.580)	0.534 (0.430, 0.662)	0.519 (0.436, 0.619)	0.591 (0.487, 0.716)	0.696 0.584, 0.830)	0.691 (0.577, 0.826)	0.633 (0.461, 0.870)	0.604 (0.434, 0.841)
	50 to 59 years old	0.459 (0.420, 0.501)	0.525 (0.479, 0.576)	0.503 (0.467, 0.543)	0.614 (0.567, 0.665)	0.747 (0.689, 0.809)	0.851 (0.785, 0.923)	0.628 (0.550, 0.717)	0.634 (0.552, 0.727)
	60 to 69 years old	0.474 (0.450, 0.498)	0.567 (0.538, 0.597)	0.533 (0.511, 0.556)	0.675 (0.645, 0.706)	0.606 (0.575, 0.640)	0.712 (0.674, 0.752)	0.742 (0.690, 0.797)	0.827 (0.767, 0.891)
	70 to 79 years old	0.485 (0.469, 0.502)	0.574 (0.555, 0.594)	0.543 (0.528, 0.559)	0.657 (0.638, 0.678)	0.637 (0.614, 0.662)	0.777 (0.747, 0.808)	0.748 (0.710, 0.787)	0.809 (0.767, 0.854)
	Older than 80 years old	0.648 (0.636, 0.659)	0.699 (0.686, 0.712)	0.684 (0.672, 0.695)	0.750 (0.737, 0.763)	0.656 (0.638, 0.676)	0.800 (0.777, 0.824)	0.879 (0.849, 0.910)	0.904 (0.872, 0.937)

3.3.6 Annual association between OA and Adverse clinical outcomes – 2004 to 2015

The annual association between OA and in-hospital mortality, MACCE, and stroke or TIA was constant over time, however the relationship between OA and all-cause bleeding appeared to change (Table 3.10). The relatively strong association between OA and a decreased odds of decreased bleeding seen in 2004 to 2006 tended to diminish towards the end of the study period (2011 onwards).

Table 3.10: The adjusted odds of adverse clinical outcomes among OA cases relative to non-OA cases stratified by year.

Year	Number of AMI cases	In-hospital mortality	MACCE	All-cause bleeding	Stroke or TIA
2004-2015	6561940	0.680 (0.670, 0.691)	0.709 (0.699, 0.719)	0.757 (0.741, 0.772)	0.844 (0.822, 0.868)
2004	596292	0.584 (0.553, 0.617)	0.619 (0.589, 0.651)	0.663 (0.619, 0.710)	0.836 (0.759, 0.922)
2005	570956	0.687 (0.651, 0.725)	0.718 (0.684, 0.753)	0.711 (0.664, 0.762)	0.892 (0.815, 0.977)
2006	580129	0.655 (0.620, 0.693)	0.693 (0.660, 0.728)	0.644 (0.600, 0.690)	0.810 (0.738, 0.888)
2007	533970	0.613 (0.579, 0.649)	0.653 (0.621, 0.688)	0.717 (0.671, 0.767	0.856 (0.777, 0.942)
2008	561863	0.700 (0.663, 0.739)	0.720 (0.686, 0.755)	0.726 (0.678, 0.776)	0.777 (0.707, 0.854)
2009	543755	0.738 (0.700, 0.777)	0.734 (0.700, 0.769)	0.700 (0.651, 0.752)	0.779 (0.710, 0.856)
2010	517049	0.756 (0.717, 0.797)	0.764 (0.728, 0.801)	0.859 (0.799, 0.923)	0.796 (0.722, 0.879)
2011	531064	0.755 (0.718, 0.795)	0.755 (0.721, 0.791)	0.916 (0.852, 0.984)	0.792 (0.720, 0.872)
2012	557605	0.655 (0.621, 0.691)	0.707 (0.674, 0.741)	0.847 (0.787, 0.912)	0.974 (0.889, 1.068)
2013	552710	0.692 (0.655, 0.731)	0.708 (0.674, 0.744)	0.869 (0.807, 0.936)	0.843 (0.766, 0.928)
2014	560890	0.680 (0.644, 0.718)	0.722 (0.688, 0.757)	0.939 (0.872, 1.011)	0.814 (0.745, 0.890)
2015	430330	0.642 (0.602, 0.684)	0.738 (0.698, 0.799)	0.823 (0.755, 0.898)	1.120 (1.020, 1.231)

3.3.7 Sensitivity analysis of the OA variable using symptomatic OA

Differences in the baseline demographics between the OA variables was discussed in section 3.2.7. Compared to the original OA group, the symptomatic OA group experienced similar likelihoods of adverse clinical outcomes including in-hospital mortality (4.7% versus 4.8%), MACCE (6.1% versus 6.1%), all-cause bleeding (2.5% versus 2.5%), and stroke or TIA (1.5% versus 1.5%) (Table 3.7).

3.3.8 Sensitivity analysis of the effect of reinfarction

After excluding patients with a previous AMI, 5,993,113 remained. Binary logistic regression showed the association between OA and each adverse clinical outcome to be nearly identical to analysis of the entire cohort (which included cases with a previous AMI) in both unadjusted and adjusted analysis (Table 3.X). This provides evidence that patients experiencing multiple hospitalisations due to reinfarction did not bias this study's results.

Table 3.11: The association between OA and adverse clinical outcome after excluding patients with a previous AMI.

	Not excluding previous AMI		Excluding previous AMI	
	Unadjusted OA	Adjusted OR	Unadjusted OR	Adjusted OR
In-hospital mortality	0.802 (0.790, 0.814)	0.680 (0.670, 0.691)	0.796 (0.784, 0.808)	0.678 (0.667, 0.689)
MACCE	0.845 (0.834, 0.856)	0.709 (0.699, 0.719)	0.841 (0.830, 0.852)	0.708 (0.698, 0.719)
All-cause bleeding	0.763 (0.748, 0.778)	0.757 (0.741, 0.772)	0.756 (0.740, 0.772)	0.752 (0.736, 0.768)
Stroke/TIA	0.996 (0.971, 1.022)	0.844 (0.822, 0.868)	1.002 (0.975, 1.029)	0.852 (0.829, 0.876)

4 Chapter 4: Discussion

4.1 Summary of results and link to previous literature

While OA has been associated with overall CVD, reports of the association between OA and AMI are conflicting. Furthermore, the effects of OA on treatments and outcomes following AMI have not been previously studied. This had guided the three aims of this study, which were to describe the prevalence of OA among AMI patients in the NIS between 2004 and 2015, to describe the association between OA and invasive management strategies following AMI, and to describe the association between OA and adverse clinical outcomes following AMI.

4.1.1 Aim 1

4.1.1.1 Prevalence of AMI

There were between 500,000 and 600,000 weighted individual admissions per year with a primary diagnosis code of AMI between 2004 and 2014 (2015 had approximately 25% fewer admissions because of the switch to ICD-10-CM/PCS starting 1st October 2015) (Figure 3.1). There were 6,651,940 cases of AMI during the study period. The annual number of people with AMI that presented to secondary care appeared stable over time and there was no apparent trend when comparing across multiple years.

The 2019 report from the American Heart Association (AHA) estimated the annual incidence of MI in 2019 to be approximately 805,000 and decreasing significantly each year (Benjamin et al., 2019). Differences between the number of AMI cases in this study and the AHA incidence estimate may be attributed to the exclusion of elective admissions. Additionally, because the NIS is an inpatient discharge database, fatal, pre-hospital AMI's were not captured, potentially highlighting a selection bias against severe cases of AMI. A study in New Zealand concluded that 24-25% of major ischemic heart disease events are fatal, of which the majority occur in the pre-hospital setting (Grey et al., 2017). Another study from Sweden with a similar sex and age distribution to this study (34.9% versus 39.8% women and mean age 70.5 versus 67.6

years) found that among 384,597 cases of AMI, 28.9% died pre-hospital (Dudas et al., 2011). Therefore, it can be reasonably assumed that 25% of AMI's in the United States are fatal in the pre-hospital setting and are not captured by the NIS, thus accounting for the fewer number of AMI cases in this study compared to the AHA annual incidence estimates. However, the exclusion of severe AMI cases means that this study's AMI cohort may have better clinical outcomes compared to the total population of AMI patients between 2004 and 2015 in the US, highlighting a lack of representativeness that may affect external validity. Despite this, accurate comparisons between this study's AMI group and the population of AMI patients who reach hospital in the United States can be made, as both groups do not include fatal pre-hospital AMI's.

Furthermore, this study's estimate of 6,651,940 AMI hospitalisations between 2004 and 2015 is similar to other studies that have used the NIS (6,968,777 AMI hospitalisations between 2004 and 2014 (Mohamed et al., 2019) and 6,563,255 AMI hospitalisations between 2004 and 2014 (Bharadwaj et al., 2019)). This, combined with AHRQ estimates of the weighted NIS being representative to 97% of all hospitalisations in the US, provides evidence that this study's sample of AMI admissions is representative to the US population.

4.1.1.2 Prevalence of OA among AMI cases

This study identified the overall prevalence of OA, as recorded by professional coders who analyse inpatient discharge summaries, to be 6.3% in the AMI group between 2004 and 2015.

This study's overall prevalence of OA among AMI patients was much lower than the estimated prevalence of OA in the general population. Among US adults over 60 years old, approximately 10% of men and 13% of women suffer from symptomatic OA (Y. Zhang & Jordan, 2010). Additionally, data from the Framingham Study estimated the prevalence of symptomatic OA to be 9.5% in patients 63-94 years-old (O'Neill et al., 2018). The mean age in this study was 67.6 years old which is similar to the aforementioned studies.

This study's low prevalence of OA was unexpected because previous studies have identified an increased prevalence of MI, heart failure, angina, and stroke in people with OA compared to people without OA (Ong et al., 2013), and a systematic review of the association between OA and CVD has shown them to be significantly linked (Hall et al., 2016). While the prevalence of OA within the general population has been extensively examined, no previous studies have identified the prevalence of OA among patients diagnosed with AMI. Given the association between OA and CVD, it is reasonable to hypothesise the prevalence of OA among AMI patients to be higher than the prevalence of OA in the general population, not lower.

Two possible explanations for the low prevalence of OA are as follows. Firstly, the exclusion of severe cases of AMI (fatal in the pre-hospital setting) may have affected this study OA prevalence estimates. One study found that of all patients suffering from a fatal pre-hospital AMI, 57% were 80 years-old or older (Grey et al., 2017). Because these patients do not make it to hospital, the NIS is potentially younger than the true population. Furthermore, age is the strongest risk factor for OA. Therefore, the NIS is likely to exclude older patients, many of whom will have OA. This selection bias is a possible explanation as to why the prevalence of OA was low within the AMI cohort. Secondly, previous studies have suggested that the prevalence of OA in EHR data may be low because of the underreporting of OA and other comorbidities in routinely collected data (Quan et al., 2002; Yu et al., 2018). Poor coding practices for OA in the NIS was evidenced in this study through the creation of a new non-binary OA variable based on anatomical location called OA sites (Appendix 6.2). Of the 5 categories of OA sites (no OA, upper limb OA, lower limb OA, generalised OA, or OA of unspecified location), the majority of people had a code for unspecified OA (81.5%). This implies OA was poorly coded in the NIS, and this may have been responsible for the low prevalence of OA among AMI cases.

This study also found that certain comorbidities were less common in people with OA compared to people without OA (Table 3.1). Particularly, people with OA tended to smoke less, were less likely to have had a previous PCI, CABG, or history of IHD, and had shorter hospital stays (4.63 (4.62, 4.65) days versus 4.86 (4.86, 4.87) days). Despite other baseline demographics that showed the OA group to have worse health than the non-OA group (they were older, and more likely to have suffered from obesity, hypertension, heart failure, and chronic lung disease), OA being associated with a better cardiovascular history and a shorter hospital stay is still unexpected given the previously mentioned associations between OA and CVD (Hall et al., 2016). Therefore, it is possible that there is a bias in the methodology of the NIS, particularly, in the coding practices of OA. The effect of these practices on the validity of OA prevalence estimates and associations between OA and clinical outcomes within the NIS is discussed further in section 4.2.

4.1.1.3 Temporal trends of OA among AMI cases

This study found that the prevalence of OA among the AMI cohort increased from 5.20% in 2004 to 7.04% in 2015 (Figure 3.3). This trend is in keeping with reports of an increasing prevalence of OA due to the ageing population and the increasing prevalence of obesity, two strong risk factors for OA (Hunter et al., 2014; Murray et al., 2012). However, most of this increase in prevalence occurred between 2006 and 2011 and the prevalence remained constant in the beginning and end of the study period (Figure 3.3). It is possible that the quality of the data has improved over time causing the prevalence to increase towards approximately 10% to 13% which is recognised to be an accurate estimate of the prevalence of symptomatic OA (Y. Zhang & Jordan, 2010). It is also possible that incentives encouraging the better coding of comorbidities such as OA may have been implemented in the years prior to 2006 which caused the steady increase of OA prevalence. Additionally, the NIS underwent a redesign in 2011 that was meant to reduce sampling error. This may have impacted the apparent increasing trend of OA prevalence prior to the redesign.

4.1.2 Aim 2

4.1.2.1 Association between OA and invasive management strategies

This study also identified that among AMI patients, those with OA were less likely to receive invasive management strategies such as CA, PCI, and CABG, even after adjustment for confounders (Table 3.5). Stratification by sex showed that it may moderate the relationship between OA and the receipt of CABG. Specifically, men with OA were more likely to receive CABG than men without OA, and women with OA were less likely to receive CABG than women without OA. Stratification by age showed that younger people with OA were more likely to undergo CABG than younger people without OA, and older people with OA were less likely to undergo CABG than older people without OA.

Previous studies have identified women, minority populations, lower socioeconomic status, and multiple comorbidities to be associated with a decreased likelihood of receiving invasive management strategies following AMI (Haglund et al., 2004; Pathak & Strom, 2008). A study using the NIS to investigate the effect of RA on outcomes following AMI found that RA patients were 39% more like to receive medical management instead of PCI or CABG (OR 1.39, 95% CI 1.30 to 1.49) (Francis et al., 2010). Other comorbidities associated with a decreased odds of receiving PCI include COPD (OR 0.5; 95% CI 0.4, 0.6) due to the inability to lay supine without coughing, end-stage renal disease (0.4; 0.3, 0.5) possibly due to the risk of contrast-induced nephropathy, diabetes mellitus (0.8; 0.7, 0.9) and alcohol abuse (0.6; 0.3, 1.0) (Pathak & Strom, 2008). A study of 961 patients diagnosed with STEMI similarly found that patients were less likely to receive PCI if they had a concurrent diagnosis of either heart failure, stroke, chronic kidney disease, anaemia, atrial fibrillation, COPD, or diabetes mellitus (Tisminetzky et al., 2015). Another study of 8831 STEMI patients found dementia to be associated with a decreased odds of CA, PCI, and CABG; the same study also found that among all patients undergoing CA, those with a diagnosis of diabetes mellitus, stroke, chronic kidney disease, heart failure, or COPD were at a decreased odds of receiving PCI (Chanti-Ketterl et al., 2014).

There do not appear to be any previous studies investigating whether the odds of receiving invasive management following AMI is affected by a diagnosis of OA. One proposed explanation for this study's result is that people with severe OA were less able to lay supine for long enough to undergo CA or PCI. Another possible explanation is that people with OA were perceived to be frail, and this perceived frailty may have biased healthcare providers away from invasive management strategies such as CA, PCI, or CABG. Overall, this study's result of OA being associated with a decreased odds of receiving CA, PCI, and CABG is congruent with the previous literature which says that comorbidities decrease a person's odds of invasive management strategies following AMI.

4.1.2.2 Annual association between OA and invasive management strategies – 2004 to 2015

The odds of people with OA receiving CA and PCI remained similar over the study period (Table 3.6). However, the odds of people with OA receiving CABG appeared to change from a decreased odds (2004 to 2009) to an increased odds (2011 to 2015).

Compared to CABG, PCI is less invasive and has been shown to have similar short-term (less than 5 years) outcomes including survival and rates of stroke and reinfarction (Stone et al., 2019). Studies of long-term outcomes have shown CABG to be superior to PCI with respect to survival and reintervention rates, however, CABG carries greater peri-operative risks (Habib et al., 2015). The EuroSCORE 2 is a risk assessment tool for estimating the risk of mortality after cardiac surgery (Nashef et al., 2012). The risk of mortality (calculated as a percent) is used by many clinicians to help decide if the benefits of cardiac surgery outweigh the risks. The EuroSCORE 2 model considers many factors that increase peri-procedural mortality including musculoskeletal dysfunction, previous AMI, previous cardiac surgery, and angina, all of which may be more prevalent in people with OA than people without OA (Nashef et al., 2012; Ong et al., 2013). Therefore, OA being associated with a decreased odds of CABG fits with the

previous literature, however, this does not explain why OA was associated with an increased odds of CABG in the second half of the study period.

4.1.2.3 Sensitivity analysis of the OA variable using symptomatic OA

Expanding this study's definition of OA to include people who suffered from joint pain, joint effusion, or previous joint replacement surgery significantly increased the prevalence of OA among AMI cases from 6.3% to 6.8% (Table 3.7). However, there were no differences between the demographics, past medical history, or the receipt of invasive management strategies between the two OA groups. Similar to the prevalence of the original OA definition, the prevalence of symptomatic OA among AMI cases was lower than the prevalence of OA in the general population. As previously discussed, it is reasonable to expect the prevalence of OA to be higher in a group of AMI patients than in the general population. This unexpected result may once again be attributed to the poor coding practices of OA in the NIS.

4.1.3 Aim 3

4.1.3.1 Association between OA and adverse clinical outcomes

This study found that AMI patients with OA had significantly better clinical outcomes than their non-OA counterparts. The results of the logistic regression modelling were that patients with OA had a decreased odds of experiencing in-hospital mortality, MACCE, bleeding, and stroke or TIA. These results persisted after adjusting for confounding variables and stratification by sex and age (Table 3.9). Negative confounding was observed in the relationship between OA and each adverse clinical outcome; the implications of this are discussed in section 4.3.3.2.

These findings directly contrast the findings of previous studies. Firstly, people with OA may be at an increased risk of all-cause and cardiovascular specific mortality (Cleveland & Callahan, 2017; Wilkie et al., 2019). Despite a lack of consensus on whether OA does predict mortality, it seems unlikely for OA to be associated with better outcomes compared to patients without OA. Secondly, people with OA are more likely to be taking NSAIDs for the relief of pain and

inflammation. Observational studies have identified NSAIDs to be associated with coronary artery disease and gastrointestinal bleeding (Farkouh et al., 2007). A limitation of the NIS is its lack of pharmacological data, meaning unmeasured confounding from medications may have significantly affected this study's result. However, unmeasured confounding through the use of NSAIDs would have increased the risk of adverse clinical outcomes such as bleeding in people with OA compared to people without OA. This further provides evidence against the validity of this study's result that OA was associated with better clinical outcomes. Finally, people with poorly managed OA are likely to avoid physical activities that may cause pain. This may lead to a decreased fitness and an increased risk of CVD and mortality (Hawker et al., 2014), further questioning this study's reported association between OA and better clinical outcomes following AMI.

A cross-sectional study published in 2010 using the NIS to investigate the effect of RA on outcomes following AMI had findings similar to this study. The researchers found that patients with RA experienced better in-hospital survival following AMI in both crude (OR 0.76, 95% CI 0.68 to 0.86) and adjusted models (AdjOR 0.66, 95% CI 0.59 to 0.74), and like this study, negative confounding was observed (Francis et al., 2010). The authors were unable to fully reconcile this finding. They suggest that RA's protective effect on mortality following AMI may be due to the RA group being 60% less likely to have heart failure compared to the non-RA controls. In contrast, a cohort study examining the effect of RA after AMI found the RA group to experience significantly higher rates of mortality (HR 1.47, 95% CI 1.04 to 2.08) and recurrent ischemia (HR 1.51, 95% CI 1.04 to 2.18) (McCoy et al., 2013). Therefore, it is likely that the apparent protective effect of RA against mortality after AMI in the Francis *et al* paper is attributed to a methodological bias. Specifically, it is possible that errors in the coding of OA and RA in the NIS have caused the spurious results seen in both the Francis et al paper and in this study.

4.1.3.2 Annual association between OA and adverse clinical outcomes – 2004 to 2015

This study found the odds of in-hospital mortality, MACCE, and stroke or TIA in people with OA to remain similar throughout the study period (Table 3.10). While OA remained associated with a decreased odds of bleeding in each year of the study period, the association was stronger in the first half of the study period compared to the second half. As previously discussed, the use of NSAIDs has been associated with gastrointestinal bleeding. The relatively higher odds of bleeding in the second half of the study period may be attributed to changes in NSAID prescription habits by primary care physicians.

4.1.3.3 Sensitivity analysis of the OA variable using symptomatic OA

Similar to the analysis of invasive management strategies, expanding this study's definition of OA to include symptomatic OA and previous joint replacement made no significant difference in the association between OA and adverse clinical outcomes (Table 3.7). A proposed mechanism explaining how misclassification bias can lead to these results can be found in the next section.

4.2 The effect of information bias in the NIS

Information bias is one explanation for some of the unexpected results in this study. The following sections discuss the potential for this with regard to the variables included in the analysis.

4.2.1 Validity of AMI codes

The validity of AMI codes are generally good; a study of 5,151 discharges from the Veterans Health Administration found the positive predictive value (PPV) of AMI codes in the primary diagnosis position to be 96.9% when using chart-abstracted data as the reference standard (Petersen et al., 1999). A similar study comparing an administrative database with chart data found that ICD-9-CM diagnosis codes for AMI had a PPV of 92.0% and a negative predictive value (NPV) of 93.1% (Quan et al., 2002). A more recent systematic review of the validity of MI

codes in EHR databases (mostly consisting of ICD-9-CM codes) found that in most studies, both the sensitivity and specificity were greater than 86% and the PPV greater than 93% (McCormick et al., 2014). The validity of ICD-9-CM codes corresponding to major illnesses (such as AMI) is high, and one can confidently infer there to be minimal information bias in this study's AMI codes.

4.2.2 Validity of invasive management codes

The validity of ICD-9-CM codes for CA, PCI, and CABG are also generally good. A comparison of discharge data versus chart data in 1200 randomly selected inpatients found similar proportions of CA (0.9% and 0.8% respectively), with a PPV of 50% and an NPV of 99.5% (Quan et al., 2004). A similar study found high sensitivities and specificities for both PCI (90.3% and 99.7%, respectively) and CABG (95.7% and 100%, respectively) (Petersen et al., 1999). Another study analysing Medicare claim data found that ICD-9-CM codes for CABG carried a specificity of 96% and PPV of 100% (Fisher et al., 1992). These results align with the existing literature in providing evidence that codes for major procedures (occurring in operating theatres) have a higher validity than codes for minor procedures performed on the ward or in radiology departments (Quan et al., 2004).

4.2.3 Validity of OA codes

While AMI and cardiac procedure codes tend to be highly valid, previous studies have found that OA is generally underreported in administrative databases (Yu et al., 2018). This is likely because OA lacks precise definitions, has a variety of phenotypes, and varies by the affected joint. All of these factors decrease the reliability of these codes and increase the likelihood of misclassification bias. As previously mentioned, the prevalence of OA is expected to increase due to the ageing population and increasing prevalence of obesity, two strong risk factors for OA (Hunter et al., 2014; Murray et al., 2012). While the prevalence of OA in this study increased over time, there was still an overall underreporting of OA, a trend that has been

observed in other studies examining OA in administrative databases. One study identified an increasing trend of the underreporting of OA in a UK primary care database, using total knee and hip replacement patients as the reference population for people with OA (Yu et al., 2018). A systematic review of the diagnostic accuracy of OA diagnoses in administrative data similarly found that OA was generally underreported, with sensitivities ranging from 29% to 83% and specificities ranging from 60% to 100% (Shrestha et al., 2016). A Massachusetts study in 2000 used a combination of medical records and an outpatient administrative database to determine the PPV and NPV of ICD-9-CM OA codes to be 62% and 78% respectively (Harrold et al., 2000). A more recent study found that a "strict" definition of OA (only using ICD-9-CM codes for osteoarthrosis, 715.xx) had a sensitivity and specificity of 34.6% and 97.5%, respectively (Cisternas et al., 2016). To increase validity, the authors also used an "expanded" definition of OA (ICD-9-CM codes 715.xx for osteoarthrosis, 716.xx for other and unspecified arthropathies, and 719.xx for other unspecified joint disorders) which increased the sensitivity (73.8%) at the cost of a slightly lower specificity (90.5%). However, the PPV of both definitions remained similar (33.5% for "strict" and 26.3% for "expanded"). The results of this "expanded OA" variable were similar to this study's symptomatic OA variable in that both definitions could not adequately encompass OA in EHR data despite including additional codes for allied disorders and symptoms. The problems associated with OA coding may be compounded in the NIS because the main incentive for accurate diagnosis coding is though reimbursement, and a diagnosis of OA is likely to be of little reimbursement value to hospitals (Khera & Krumholz, 2017).

4.2.4 Validity of comorbidity codes

Osteoarthritis is not the only chronic comorbidity described to be underreported in EHR data. A study comparing an ICD-9-CM coded administrative database to hospital chart data in a random sample of 1200 patients found that there was a general underreporting of Charlson comorbidities in the administrative database (Quan et al., 2002). The Charlson comorbidities

that were most significantly underreported included rheumatological disease, cerebrovascular disease, dementia, diabetes with chronic complications, peptic ulcer disease, and peripheral vascular disease. A similar study comparing the coding accuracy of Charlson comorbidities found there to be a low correlation (kappa = 0.47) between the comorbidities documented in administrative data and chart data (Kieszak et al., 1999).

4.2.5 Further decline in comorbidity code validity in unwell patients

The problem of comorbidities being underreported in administrative data tends to worsen when patients are unwell or die in-hospital. In a cohort of 817 patients undergoing PCI, concordance between chart data and administrative data was poor for chronic comorbidities including diabetes (17.6% versus 14.7%), hyperlipidaemia (40.5% versus 14.9%), and hypertension (41.1% versus 27.5%) (Humphries et al., 2000). The authors also noted that asymptomatic conditions generally had the lowest level of agreement. Another study examined 162,790 discharges in California in 1988 to investigate the effect of secondary diagnoses on death among a group of elderly patients hospitalised for stroke, pneumonia, AMI, or heart failure (Iezzoni et al., 1992). The study found that AMI patients were associated with better in-hospital survival if they had a concurrent diagnosis of hypertension (relative risk 0.57, $p<0.0001$), previous AMI (0.84, $p<0.01$), angina pectoris (0.41, $p<0.0001$), COPD (0.89, $p<0.05$), or ventricular premature beats (0.49, $p<0.0001$). It is unlikely that there is a biological mechanism causing these comorbidities to confer better in-hospital survival. The authors attributed this result to a coding bias, where the patients who died were less likely to have codes for chronic comorbidities because they were replaced by codes for acute complications relating to death, such as cardiac arrest or respiratory failure. Additionally, the authors referenced ICD-9-CM coding guidelines that suggested that diagnoses that have no bearing on the current hospital stay should be excluded.

The previously mentioned study did not examine the association of OA on in-hospital mortality, however, a very similar study found that in patients over 65 years-old diagnosed with AMI, those with a concurrent diagnoses of OA (and many other chronic comorbidities) experienced significantly lower rates of short and long term mortality (Jencks et al., 1988). The conditions with the strongest associations to lower short-term in-hospital mortality were obesity (odds ratio 0.33, $p<0.0001$), OA (0.33, $p<0.0001$), benign prostatic hyperplasia (BPH) (0.35, $p<0.0001$), diverticulosis (0.39, $p<0.01$), and hypertension (0.48, $p<0.0001$). The authors argued that this relationship is clinically highly unlikely and may be attributed to the underreporting of chronic conditions in unwell patients (such as those diagnosed with AMI). They hypothesised that this underreporting of comorbidities occurs because ICD-9-CM codes associated with death (such as cardiac arrest) took precedence over codes for chronic comorbidities (such as OA). They provided evidence for this by arguing that the chronic conditions with the lowest likelihood of affecting mortality (OA and BPH) should not have had the strongest associations with better survival.

Although the previous two studies were published many years ago, they were the only studies found to investigate the prognostic effect of comorbidities (such as OA) on the outcomes following AMI. It is possible that the bias identified in these studies had similar effects on the results of this study.

4.2.6 Systematic differential misclassification bias

This study has suggested that OA was underreported among AMI patients in the NIS, as only 6.8% of the cohort was identified using the "symptomatic" definition of OA. This result aligns with the previously reported hypothesis that there is a significant underreporting of comorbidities (including OA) among unwell patients (such as those suffering from AMI) in EHR data. This hypothesis is further supported by the results of this study's binary logistic regression, which implied that people with OA experienced better clinical outcomes than

people without OA. A biological mechanism explaining this result is highly unlikely because previous studies have associated OA with an increased risk of CVD. A chronic condition like OA is likely to increase one's risk profile (or at the minimum exert no effect) and should not be "protective" against adverse clinical outcomes. Therefore, the most likely explanation for OA being associated with better clinical outcomes is a **systematic, differential misclassification bias, where OA patients who experienced adverse clinical outcomes (i.e. are "unwell") were less likely to receive a code for OA.** This misclassification occurred because codes associated with serious illness and death took precedence over OA codes. Because the unwell OA patients were potentially removed from the true OA cohort and were misclassified as not having OA, this study's OA group may have been "healthier" than the non-OA group. This makes it reasonable to expect the OA group to have better clinical outcomes than the non-OA group, and implies that OA is adequately reported in well patients but underreported in those that are unwell. This is evidenced in Table 3.1 which showed that people with OA tended to smoke less, were less likely to have had a previous PCI, CABG, or history of IHD, and had shorter hospital stays (4.63 (4.62, 4.65) days versus 4.86 (4.86, 4.87) days). However, Table 3.1 also showed the OA group to have characteristics that are normally associated with worse clinical outcomes, including advanced age (mean age 75.3, SD 12.3; versus 67.1, SD 14.4 years-old) and the higher prevalence of certain comorbidities (including hypertension and chronic lung disease). Despite these characteristics generally conferring worse clinical outcomes following AMI, it is hypothesised that the effect of misclassifying the subset of OA cases that were very unwell as not having OA was great enough to confer better outcomes in the OA group. Therefore, the cases that remained in the OA group had better clinical outcomes because of the removal of the severe cases from the cohort, despite the OA group also being older and having a higher prevalence of certain comorbidities.

4.3 Strengths and limitations

4.3.1 The NIS

There are many benefits to using the NIS. Firstly, it is the largest publicly available all-payer database in the United States, recording over 7 million unweighted hospital admissions per year, with each admission including up to 30 diagnosis and 15 procedure codes (Healthcare Cost and Utilisation Project, 2019). The large number of admissions within the NIS allows for precise estimates and the study of rare diseases that are difficult to study using small datasets. Additionally, according to HCUP, the number of annual peer-reviewed articles studying the NIS has sharply increased from 100 in 2006 to 550 in 2016 (Khera & Krumholz, 2017). Secondly, as previously discussed, the NIS has good quality information on AMI and invasive procedures such as CA, PCI, and CABG, allowing for accurate analyses of these variables. Finally, weights may be applied to the NIS's 20% sample to produce estimates that are representative to the entire inpatient population of the United States (Healthcare Cost and Utilisation Project, 2019). The NIS's sampling method ensures that it is representative to the US population with respect to diagnosis-related groups (DRG), admission month, and hospital level factors including location, size, and teaching status (Healthcare Cost and Utilisation Project, 2014). All these factors contribute towards good external validity when studying the NIS.

The NIS inherently comes with several limitations. Firstly, as previously mentioned, a consequence of the 2012 redesign was the removal of patient identifiers in order to enhance patient confidentiality. This means that multiple hospital discharges within the dataset may be attributed to the same individual (Khera & Krumholz, 2017). This design change was significant for patients with conditions causing recurrent hospital visits (for example chronic lower respiratory diseases) because of the inability to track multiple admissions from the same patient. Despite AMI not being a relapsing and remitting condition, a significant proportion of patients suffer from reinfarction. One study found that after a person's first AMI, there was a

6% reinfarction rate over one year (Kornowski et al., 1993), while another study found reinfarction rates for PCI managed and medically managed AMIs to be 9.4% and 8.0%, respectively, over 7 years (White et al., 2012). Therefore, recurrent admissions from patients suffering from reinfarction had the potential to introduce bias into this thesis' results. However, the analysis performed in section 3.3.8 provided evidence that the effect of people being admitted multiple times due to reinfarction was unlikely to have biased this study's results. Secondly, the NIS does not contain information on the severity of AMI, which may have differed by OA status. Thirdly, the AHRQ estimated that the NIS redesign caused a 4% decrease in the total number of discharges in 2012 compared to 2011, potentially leading to inaccuracies when analysing temporal trends (Healthcare Cost and Utilisation Project, 2019). This one time decrease in the total number of discharges did not appear to affect this study's analysis, as the number of AMI patients remained similar throughout the study period. Fourthly, the NIS only contains routinely collected data encompassing a patient's hospitalisation and does not contain information about the patient's follow-up appointments or outpatient visits. The final drawback is the lack of medication data stored within the NIS, which is discussed in section 4.3.3.1.

4.3.2 Study design

This thesis was limited to a cross-sectional study design due to the lack of follow-up data on each hospitalisation record. Diagnosis codes were generated upon discharge from hospital, thus making it impossible to know with certainty whether a diagnosis code is referring to a pre-existing comorbidity or a complication that developed during the hospital stay (Bharadwaj et al., 2019). We therefore cannot comment on whether OA caused better or worse outcomes in patients following AMI, we may only comment on associations. Further cohort studies are required to make assertions about temporality in the relationship between OA and treatments and outcomes following AMI.

4.3.3 Confounding

4.3.3.1 Unmeasured confounding

Unmeasured confounding, defined as the omission of a relevant confounder from a model (Fewell et al., 2007), may have affected this study's results. The NIS does not contain medication data, and because this could not be adjusted for in logistic regression modelling, medication data is a potential source of unmeasured confounding. This may be particularly problematic when studying the association between OA and CVD because the use of oral NSAIDs confounds their relationship. Oral NSAIDs are commonly taken by people with OA because they are effective in relieving joint pain and inflammation. However, oral NSAIDs have serious side effects including gastrointestinal tract ulcers, reductions in glomerular filtration rate, and cardiovascular risks including hypertension, myocardial infarction, and stroke (Varga et al., 2017). Therefore, the regular use of NSAIDs is likely to place people with OA at an increased risk of adverse clinical outcomes (including stroke, MACCE, and bleeding). However, the opposite association was observed in this study, providing further evidence of a systematic differential misclassification bias being responsible for the observed protective effect of OA. Another potential unmeasured confounder is frailty. This study found OA to be associated with a decreased odds of receiving invasive management including CA, PCI, and CABG. A possible explanation for this association is that people with OA appear to be frail, and this perceived frailty may make healthcare providers more hesitant in offering invasive managements. The effect of other unidentified unmeasured confounders may also have biased this study's results.

4.3.3.2 Negative confounding

Negative confounding was seen in the regression analyses between OA and each adverse clinical outcome (Table 3.9). In order to determine the source of the negative confounding, the adjusted binary logistic regression models were built by adding one covariate at a time. This identified most of the negative confounding to be attributed to demographic factors, particularly age. As an example, consider the relationship between OA and in-hospital

mortality. The crude OR of the association between OA and in-hospital mortality was 0.802 and the adjusted OR was 0.680. When only OA and age were included as independent variables in the model, the OR was 0.567. This implies that in this study age was a negative confounder and thus differently associated (either direct or inverse) with OA (the "exposure") and in-hospital mortality (the "outcome"). However, common knowledge and previous studies have shown age to be strongly positively associated with OA and with mortality following AMI (Mehta et al., 2001; Vina & Kwoh, 2018; Y. Zhang & Jordan, 2010). Additionally, this study showed that OA patients were older (75.3 (SD 12.3) versus 67.1 (14.4) years-old) than people without OA, and people who died were older than people who survived (76.0 (12.7) versus 67.1 (14.3) years-old), providing further evidence that age is positively associated with OA and with mortality.

It remains unclear why age-adjusted estimates tended further from the null than crude estimates when considering the relationship between OA and in-hospital mortality. This may be due to age exerting a different effect on OA and mortality depending on the age that is considered. Interestingly, further model building strategies found age to have a similar relationship between OA and the remaining adverse clinical outcomes, including MACCE (crude OR: 0.845; age-adjusted OR: 0.608), all-cause bleeding (crude OR: 0.763; age-adjusted OR: 0.643), and stroke or TIA (crude OR: 0.996; age-adjusted OR: 0.795).

4.4 Implications

4.4.1 Future research

The most important implication of this work is its critique of the validity of comorbidity codes in large administrative databases. The findings from this study suggest the validity of comorbidity codes is lower than primary diagnosis codes in the NIS. The validity of codes for comorbidities with imprecise definitions like OA are even poorer, as are codes for patients who are acutely unwell because more serious codes take precedent. These considerations are

relevant to not only the NIS but all EHR databases, as this bias has been reported in previous studies of OA and acute illness in large administrative databases (Jencks et al., 1988; Yu et al., 2018). However, this bias is likely to be worse in secondary care versus primary care EHR databases because patients presenting to primary care with acute illnesses are often transferred immediately to secondary care. Therefore, it is important to exercise caution when analysing secondary care comorbidity data, especially in unwell patients. Researchers must also ensure the validity of OA coding practices within their database in order to avoid potential information biases and to facilitate better research.

No previous studies have examined the association between OA and outcomes other than death (such as MACCE, bleeding, stroke, or the receipt of invasive management strategies) following AMI. Therefore, this study presents novel findings of the association between OA and treatment and outcomes following AMI. However, there is still a need for further research into this topic because of the bias that is likely to have obscured this study's results. Previous studies using EHR data have similarly observed misclassification bias when analysing comorbidity data in acutely unwell patients (Iezzoni et al., 1992; Jencks et al., 1988). These difficulties are likely inherent to all EHR databases as there is always a degree of misclassification. An alternative way to investigate this research question may be through a cohort study design that uses questionnaires that are linked to medical records. However, this comes with its own difficulties because patients may not be able to accurately recall the details of hospital visits. Future research may also focus on very similar questions in order to elucidate the precise reason for the bias. For example, would the misclassification bias observed with this study's OA codes remain if a less serious illness such as angina pectoris was studied instead of AMI? Alternatively, future studies can investigate whether other chronic comorbidities (such as hypertension or BPH) experience the same misclassification bias as OA following AMI. Additionally, it has been shown that comorbidities more serious than OA such

as RA are also likely to be subject to information bias when being associated with mortality following AMI (Francis et al., 2010).

4.4.2 Clinical practice

This study found that people with OA were less likely to receive invasive management strategies and less likely to experience adverse clinical outcomes following AMI compared to people without OA. People with OA are already a target group for health promotion strategies because of the association of OA with comorbidities. Clinicians should also be aware of the potential inequality that people with OA have with respect to the availability of invasive management strategies following AMI. A possible explanation for people with OA being less likely to receive invasive management is that people with severe OA are less able to lay supine for long enough to undergo CA or PCI. An awareness of the barriers to invasive management strategies may improve outcomes following AMI for people with OA.

Additionally, women were identified to be more likely to suffer from adverse clinical outcomes than men. In order to address this inequality in care, clinicians should consider why this is may occur. Women are more likely to present with atypical AMI symptoms such as neck pain, back pain, jaw pain, and nausea, and are less likely to present with chest pain and diaphoresis (Goldberg et al., 1998). These atypical symptoms may cause delays in diagnosis and potentially cause women to experience worse outcomes following AMI compared to men.

Finally, this study found that both men and women with OA were associated with better clinical outcomes compared to people without OA. However, because of the misclassification bias hypothesised to be affecting this study, clinical practice should not be changed to reflect this finding. Previous studies have shown OA to be associated with poorer health related outcomes, therefore, more research into the effect of OA on outcomes following AMI must be conducted before clinical practice should be affected.

4.5 Conclusion

There is an association between OA and overall CVD, however, the association between OA and AMI is less clear. This study identified that people with OA were less likely to receive invasive management strategies and were, unexpectedly, more likely to have better outcomes following AMI compared to people that did not have OA. This unexpected result is likely to be partially attributable to a systematic differential misclassification bias where people with OA were classified as not having OA because precedence was given to diagnosis codes for acute illness. Future research into the association between OA and AMI using secondary care EHR databases must take this potential bias into account.

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6 Appendix

6.1 ICD-9-CM codes used in this study

Table 6.1: Table of ICD-9-CM codes.

Acute myocardial infarction (410.xx)		
	Anterolateral	410.0x
	Anterior	410.1x
	Inferolateral	410.2x
	inferoposterior	410.3x
	Inferior	410.4x
	Lateral	410.5x
	Posterior	410.6x
	Non-ST elevated MI	410.7x
	Other specified sites	410.8x
	Unspecified site	410.9x
Osteoarthritis (715.xx)		
	Generalised OA	715.0x, 715.8x
	Upper limb OA	715.11-4, 715.21-4, 715.31-4, 715.91-4
	Lower limb OA	715.15-7, 715.25-7, 715.35-7, 715.95-7
	Unspecified	715.10, 715.18, 715.20, 715.28, 715.30, 715.38, 715.90, 715.98, V134
Pain in joint		719.4x
Effusion of joint		719.0x
Joint replacement		
	Total shoulder arthroplasty	81.80
	Shoulder hemiarthroplasty	81.81
	Reverse total shoulder arthroplasty	81.88
	Total hip arthroplasty	81.51
	Total knee arthroplasty	81.54

	Total ankle arthroplasty	81.56
	Ankle fusion	81.11
	Ankle arthrodesis	81.12
	Total elbow arthroplasty	81.84
Invasive management strategies		
	Coronary angiography	88.52, 88.53, 88.54, 88.55, 88.56, 37.22, 37.23
	Percutaneous coronary intervention	00.66, 36.01, 36.02, 36.06, 36.07, 36.09
	Coronary artery bypass grafting	36.1x, 36.20, 36.31, 36.32, 36.9x
Adverse clinical outcomes		
	In-hospital mortality	Recorded in the NIS
	Major acute cardiovascular and cerebrovascular events	Haemopericardium (423.0), cardiac tamponade (423.3), pericardiocentesis (37.0), coronary dissection (414.12)
	All-cause bleeding	Gastrointestinal haemorrhage (578.0, 578.1, and 578.9), intracranial haemorrhage (430, 431, and 432.x)
	Stroke and TIA	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, 436
Past cardiovascular history		
	Previous AMI	412.xx
	Previous PCI	V45.82
	Previous CABG	V45.81
	Previous stroke	V12.54
	History of IHD	414.00-07, 414.2-9
	Smoking status	V15.82, 305.1

6.2 OA sites

A categorical variable called “OA sites” was created based on the anatomical site of OA. The ICD-9-CM 715.xx codes from Appendix 1 were used to stratify the AMI cohort into the five anatomical OA subtypes, no-OA, upper limb OA, lower limb OA, generalised OA, and unspecified OA. Cases that had codes for two different OA sites were excluded from this variable, leaving cases that only have OA in a single site.

Of all AMI cases, 414,072 (6.3%) cases of OA were identified. After excluding people with multiple subtypes of OA (n=3,063), 411,009 (6.3%) cases of OA remained to be analysed by site. Of these remaining cases, 10,057 (2.4%) had upper limb OA, 46,132 (11.2%) had lower limb OA, 19,820 (4.8%) had generalised OA, and 335,000 (81.5%) had OA of unspecified location and type.